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ORIGINAL ARTICLES.

THE NATURE OF THE HEMORRHAGIC DISEASE OF THE NEWBORN.

DELAYED RESTORATION OF THE PROTHROMBIN LEVEL.

BY ARMAND J. QUICK, PH.D., M.D.,
ASSOCIATE PROFESSOR OF PHARMACOLOGY, MARQUETTE UNIVERSITY SCHOOL OF MEDICINE,

AND

ARTHUR M. GROSSMAN, M.D.,
ST. MARY'S HOSPITAL, MILWAUKEE, WIS.

(From the Department of Pharmacology, Marquette University School of Medicine, and St. Mary's Hospital.)

KNOWLEDGE concerning the danger of hemorrhage in the newborn dates back to ancient times. In Genesis one finds the Mosaic law specifically setting the eighth day after birth as the time for circumcision, and numerous repetitions of this law are found both in the Old and New Testament. Even now circumcision and other operations are usually postponed until the baby is a week old. Nevertheless, this potential danger of hemorrhage is not clearly and generally recognized since excessive bleeding is relatively rare. When hemorrhage does occur in babies, it is usually looked upon as a distinct clinical entity to which has been given the name "hemorrhagic disease of the newborn."

The existence of a bleeding disease in newborn infants was first reported in the European literature by Mauriceau[16] in 1682. Umbilical bleeding was reported by Watts[31] in 1753, and Cheyne[6] recorded a case in 1801. The disease was also described in a treatise by Capuron[5] in 1820. H. J. Bowditch,[2] apparently the first American

who published studies of the hemorrhagic disease in babies, recognized the possibility that umbilical bleeding was perhaps only one manifestation of a hemorrhagic diathesis. F. Minot[17] presented a similar view in a paper published 2 years later, and suggested that jaundice might be an etiologic factor as he found a frequent association of bleeding with icterus. The concept that umbilical bleeding was a part of a more general bleeding tendency was further established by the work of Coale[8] and Thayer.[26] In 1894 appeared the classical paper of Townsend,[27] in which he named the syndrome "the hemorrhagic disease of the newborn." He furthermore clearly differentiated this condition from hemophilia and emphasized the fact that the disease was self-limited. He believed that infection was the cause. The further minor developments in the recognition of this disease have been adequately summarized by Gelston,[9] and Lövegren[13] has reviewed the literature on melæna neonatorum.

The cause of the hemorrhagic disease in newborn babies baffled the early investigators, and little that was in any way helpful in determining the basic factors responsible for the bleeding was contributed by subsequent workers. Minot listed as possible etiologic factors: hereditary predisposition, sex, liver dysfunction, and imperfect closure of the umbilical vessels. Townsend, as already mentioned, considered the disease of infectious origin. In 1912, Schloss[23] summarized the prevailing views of the disease. He pointed out that the bleeding may be due to hemophilia, infection, congenital syphilis, gastric or duodenal ulcers, a defect in the coagulation mechanism such as a deficiency of fibrinogen, diminution of thrombin, or to localized vascular lesions. Schloss and Commiskey[24a] somewhat earlier had reported that in the hemorrhagic condition of the newborn, coagulation may be normal, delayed, or absent. In retrospect, the most important observation was that of Whipple[33] who found a complete absence of prothrombin in a fatal case of this disease. Unfortunately, the test was made on postmortem blood. Furthermore, knowledge concerning the coagulation mechanism was in such a confused state at that time that his findings could not be properly evaluated.

In 1921 Rodda[21] made the interesting observation that the coagulation time of babies had a tendency to increase after birth, reaching the maximum retardation on the fifth day, but returning to normal before the tenth day. Lucas and his associates[14] confirmed these observations. No satisfactory explanation for these findings could be offered. Sanford and Leslie[22] came to the conclusion that the platelets were more resistant to disintegration in this hemorrhagic disease.

Since the cause of the hemorrhage in infants was not known, treatment could not be specific. Minot and the other early investigators attempted merely to treat the bleeding locally with styptics and astringent agents. The injection of gelatin solution was used,

especially by European clinicians.[13] In 1908 Lambert[12] successfully treated a bleeding baby with a direct transfusion of blood. Welch[32] a little later reported a series of 12 cases treated both by direct transfusion and by subcutaneous injection of blood. Schloss and Commiskey[24a] introduced the method of injecting small amounts of blood intramuscularly. The authors, however, recognized the difficulty of evaluating the efficacy of this treatment because of the fact that spontaneous recovery could occur. In fact, they reported in a later paper[24b] a case in which the baby died in spite of the treatment with several injections of blood. Soresi[25] advocated direct transfusion as the best method. Nevertheless, the injection of whole blood intramuscularly became a widely accepted therapeutic measure. Sanford and Leslie recently challenged the value of this method and advocated intravenous transfusion as the preferred means of giving blood.

With the recognition of the importance of prothrombin deficiency as a cause of hemorrhage, and the discovery that vitamin K is essential for the synthesis of this clotting factor, came a new approach to the study of hemorrhagic disease of the newborn. In 1935 Quick[19a] described a quantitative method for prothrombin and showed that this clotting agent was markedly diminished in certain jaundiced patients. A year later Warner, Brinkhous and Smith[29] adopted the principle of Quick of adding an excess of thromboplastin and developed a second method for determining prothrombin. Instead of completing the test in one step, they determine the dilution of the plasma which with thromboplastin and calcium will clot a solution of fibrinogen in 15 seconds, and they express the concentration of prothrombin in terms of this dilution factor. By means of their method, Smith and his associates[3] found almost a complete absence of prothrombin in a case of severe bleeding that occurred in a newborn infant, which confirmed the earlier observation of Whipple. Oddly, however, when they applied their method to the study of normal infants' blood, they found astonishingly low values. In 4 babies, 5, 8, 8, and 11 days old, the prothrombin concentration was 36, 44, 27 and 37% respectively, and even babies 2 months old still had a prothrombin level of only 42% of normal. These results suggest that all babies are in potential danger of hemorrhage during the first few weeks of life, which is not in accord with clinical observations.

Since the methods of both Smith and his associates, and of Quick are based on unproved assumptions, it is possible to evaluate them only in terms of their correlation with clinical and experimental findings. In regard to Quick's method, it has been found to be a delicate measure of the prothrombin concentration in the blood of jaundiced patients and promptly shows the response to vitamin K therapy.[19d] Likewise in experimental studies of vitamin K deficiency in chicks[19b] and in rats[10] the procedure showed a progressive

drop of prothrombin, and a restoration to normal when the vitamin was supplied. In chloroform poisoning in dogs, a severe fall in prothrombin was also found with this method.[19c] In sweet clover disease[19b] the method demonstrated the continuous drop in prothrombin, and the accuracy of the determination was shown by the fact that when the prothrombin reached a certain level the animal invariably died from a hemopericardium if blood was taken by heart puncture. Recently the method was employed to demonstrate prothrombin deficiency in various intestinal disorders and to show the response to vitamin K therapy.[4] Thus, the method of Quick has given satisfactory results in the study of all hemorrhagic diseases characterized by a deficiency of prothrombin. In many conditions, moreover, this method yields results which run parallel with those obtained with Smith's procedure. It seemed therefore desirable to study the prothrombin concentration of the blood of newborns with Quick's method.

TABLE 1.—QUANTITATIVE DETERMINATION OF PROTHROMBIN.

Concentration of prothrombin in plasma, %	Clotting time.* Undiluted plasma, sec.	Clotting time.* Diluted plasma,† 50%, sec.
100	11–12	15
97	..	15½
90	..	16
85	..	16½
80	12½	17
75	..	17½
70	..	18
67	..	18½
65	..	19
60	13½	19½
58	..	20
56	..	20½
53	..	21
50	15	21½
40	17	
30	19½	
25	22	
20	25–26	
10	37–40	
5	55–65	

* Oxalated plasma, 0.1 cc., is mixed with 0.1 cc. of thromboplastin solution, and recalcified with 0.1 cc. of 0.025 M calcium chloride. The clotting time is determined at 37.5° C.

† The plasma is diluted with an equal volume of physiologic saline solution.

Procedure. Blood was drawn from the internal jugular vein. Usually 1.8 cc. of blood were taken and mixed immediately with 0.2 cc. of 0.1 M sodium oxalate. The plasma was analyzed for the prothrombin content by the method described previously.[19c] Since the variations in clotting time between 50 and 100% are very small, greater accuracy is obtained by diluting the plasma with an equal volume of physiologic saline solution, and then determining the clotting time of the 50% plasma (Table 1).

It has been found that if the thromboplastin which is prepared by the acetone method is kept in evacuated glass ampules, no loss of activity occurs.

Results. The results are summarized in Chart 1. At birth the concentration of prothrombin is relatively high, about 60 to 75% of the normal adult value. The series, however, is too small to conclude that the prothrombin is nearly normal in all newborn infants, but the fact that the analysis of a great number of cord bloods (placental) gave values of 60 to 70% suggests that the prothrombin in the baby at birth is fairly high. Soon after birth, however, the prothrombin decreases, and may reach exceedingly low levels. In the babies studied, the prothrombin was lowest the first day, somewhat higher during the second day, and almost always normal after the third day. Since these results were first reported,[20] Waddell and Guerry,[28] and Owen, Hoffman, Ziffren and Smith[18]

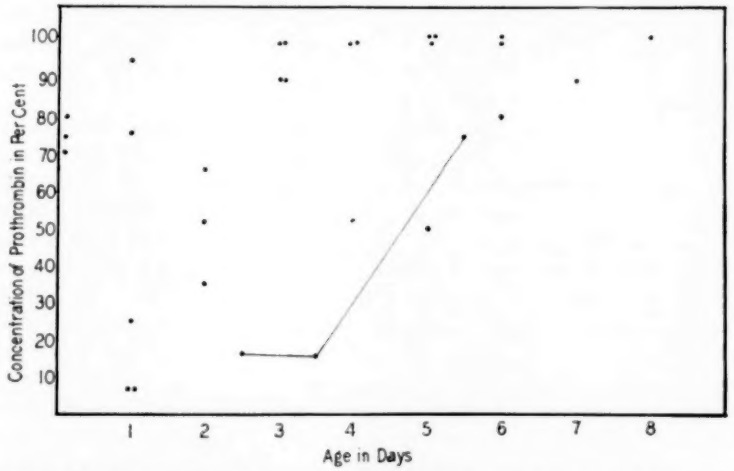

CHART 1.—The prothrombin concentration in the blood of newborn infants. All babies were in good health. One baby with a prothrombin of 7% had mild umbilical bleeding. The points connected by lines show the restoration of the prothrombin in one infant.

(both groups using Quick's method) obtained similar results with the exception that the drop in prothrombin usually came on the second and third days and returned to normal after the fifth day.

From the results obtained, it can be concluded that at birth the prothrombin in the baby's blood is relatively high, but often drops precipitously during the first days of life, and then, strangely, is spontaneously restored. Immediately, an answer is suggested to the question of the origin of the hemorrhagic disease of the newborn. The frequency with which the prothrombin falls in normal infants makes it highly probable that all infants are in danger of hemorrhage during the first few days of life. In the recognized hemorrhagic disease of the newborn, it is very likely that the fundamental cause is a delay in the spontaneous restoration of the prothrombin level. It

will be recalled that Townsend in 1894 clearly stated that the disease was self-limited. Thus, it seems that the hemorrhagic disease of the newborn is a potential threat to all infants. Consequently, if an infant should bleed accidentally, the small loss of blood may be sufficient to reduce the prothrombin level which is already low to a point where hemorrhage becomes difficult to control, and a vicious circle is initiated.

The cause of the prothrombin deficiency seems to be due to an inadequate storage of prothrombin or of vitamin K in the fetus. Presumably as soon as the baby is born, the physiologic demands promptly exhaust the available prothrombin. Since there is apparently neither a reserve of vitamin K nor of prothrombin, a marked decrease of the latter occurs. The condition is clearly due to a lack of vitamin K, for not only can the prothrombin be promptly restored to normal by giving the baby a concentrate of this vitamin, but also the serious fall in concentration can be prevented by the oral administration of this food accessory substance.[28]

This leads to the interesting speculation concerning the spontaneous recovery of the prothrombin level in normal infants. Since the drop in prothrombin is distinctly a manifestation of vitamin K deficiency, the rise must be due to a supply of this vitamin which was not present at birth. In view of the fact that the food intake during the first few days is scarcely sufficient to assure an adequate supply of vitamin K, another source must be sought. As is well known, especially from Almquist's[1] work, bacteria readily synthesize vitamin K. At birth the intestinal contents of the baby are sterile, but in a very short time, especially if the baby is allowed to suckle, bacteria are introduced, and an intestinal flora is established. The time relation between the beginning of bacterial activity and the restoration of the prothrombin level makes it appear likely that the available vitamin K is of bacterial origin. This explains adequately the rather puzzling finding of Javert[11] that the incidence of hemorrhagic disease of the newborn in a large series of cases was over twice as high in the New York Hospital as in the outdoor service of the Berwind Free Maternity Clinic. The babies born under the far less sanitary conditions of the home or tenement had a chance to infect their intestinal tracts sooner than the babies born under the ideal conditions of a modern hospital. Perhaps the practice of putting the baby to the breast early serves the primary purpose of introducing harmless but useful bacteria into the alimentary tract.

While one can only speculate on the cause of the fall of prothrombin and its rather prompt restoration in normal infants, the fact seems well established that even a healthy infant with no visible signs or symptoms may have for a short period an astonishingly low concentration of prothrombin in its blood. With this concept, a concise delineation of the hemorrhagic disease of the newborn can now be presented. Only a few months ago Clifford[7] wrote: "The

diagnosis of hemorrhagic disease can only be made on clinical grounds until its etiology is established, in the absence of characteristic pathology or consistent laboratory findings." Now the diagnosis can be made by laboratory means, before the child shows clinical signs, and the chief etiologic factor can be considered as a deficiency of prothrombin due to absence of vitamin K. The conclusion of Clifford that the hemorrhagic disease is a loose clinical syndrome and not a true disease entity no longer holds and the confusion concerning the disease, which this author discusses at length, can be cleared.

The hemorrhagic disease of the newborn is clinically recognized by external or internal hemorrhage occurring during the first few days of life; is characterized by an exceedingly low prothrombin content of the blood; is usually self-limited but may be fatal; and is promptly cured by vitamin K. It is probable that the disease may be precipitated by a small hemorrhage, thus further reducing the depleted prothrombin as already discussed. Although no positive proof exists that cerebral hemorrhage in babies following delivery is one form of the "hemorrhagic disease," it seems very likely that it is, and that the lowered prothrombin is the important factor. If the latter clotting agent were normal in amount, the excess of thromboplastin which is present in the brain would speedily stop hemorrhage.

With these considerations, attention can be turned to the prevention and treatment of the disease. Since no evidence exists that the baby is born with a marked deficiency of prothrombin, the important problem to be solved is the prevention of the fall in the clotting factor. Waddell and Guerry have demonstrated that this can be accomplished by administering vitamin K orally. But in the normal infant, this hardly seems necessary. Perhaps a return to the practice of early breast feeding will be sufficient. But in any case of difficult labor in which intracranial injury is likely to occur, the oral administration of a concentrate of vitamin K should begin immediately and be continued for several days. Vitamin K should also be given promptly if slight oozing is noticed from the umbilical cord or any other small wound, or if blood appears in the stool or urine. Unless the hemorrhage is severe, a direct blood transfusion need not be given since vitamin K acts very promptly. Whether intramuscular injection of blood is of any value has never been satisfactorily answered.

Jaundice in the newborn is not a contributing factor, for a number of babies who were distinctly icteric had a normal prothrombin level, whereas babies that had shown a low prothrombin level had no evidence of bile in the blood. Furthermore, a case with congenital atresia of the common bile duct reported earlier[19c] showed a normal prothrombin, and another baby 5 weeks old that was jaundiced from birth likewise had a concentration of 100% normal. Watkins and Wright[30] found that a baby who survived 15 months with

congenital atresia of the bile duct had a normal coagulation time. It appears that when the normal prothrombin level is once established in the baby, it becomes difficult to cause any appreciable diminution. It is therefore usually possible to operate on a child after it is a week old without danger of untoward bleeding. If it is imperative that an operation be performed earlier, the prothrombin should be determined by Quick's method, and if it is found low, vitamin K should be given preoperatively.

With this new concept of the hemorrhagic disease of the newborn, rapid progress can be expected. The prevention of the prothrombin decrease after birth is of particular importance and warrants further study. While it appears likely that the vast majority of bleeding cases will be found to be due to prothrombin deficiency, it must be recognized that other types of hemorrhagic diatheses may be encountered. Congenital absence of fibrinogen, although exceedingly rare, can be the cause of bleeding.[15] Hemophilia, perhaps, rarely manifests itself immediately after birth, but theoretically must be considered. It is interesting that the 2 cases reported by Bowditch are not altogether typical of hemorrhagic disease of the newborn, as this clinical entity is now recognized. In his cases, the hereditary factor seemed most important. According to present concepts, a definite diagnosis can only be made by establishing a low prothrombin by laboratory tests, or by curing the disease with vitamin K. If these two diagnostic tests are negative when applied to an unknown bleeding condition, it does not belong to the disease presented in this paper.

Summary. It has been found that the prothrombin concentration of infants' blood is nearly at the same level at birth as that of the adult. It often drops, however, abruptly during the first few days of life, but is restored spontaneously and usually promptly to normal. The suggestion is made that the recovery of the prothrombin concentration is brought about by the establishment of a bacterial flora in the intestines, and that this initiates the synthesis of vitamin K which becomes available to the organism of the infant for the production of prothrombin.

The hypothesis is presented that the cause of the hemorrhagic disease of the newborn is due to a delayed restoration of the prothrombin level, and the disease is defined as one which is clinically recognized by external or internal bleeding; is characterized by an exceedingly low prothrombin concentration in the blood (as determined by the method of Quick); is usually self-limited, but may be fatal; and is promptly cured by the oral administration of vitamin K.

Since this paper was submitted, Nygaard (Acta Obst. et Gyn. Scand., **29**, 361, 1939) reported that the prothrombin is normal at birth but begins to drop during the second half of the first day. He further reports that vitamin K prevents this fall in prothrombin. Three cases of bleeding in the newborn responded promptly to vitamin K given orally.

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BLOOD STUDIES ON THE NEWBORN.

II. Direct and Total Blood Bilirubin: Determinations over a Nine-day Period, with Special Reference to Icterus Neonatorum.

By Theo. R. Waugh, M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, MC GILL UNIVERSITY; PATHOLOGIST, ROYAL VICTORIA HOSPITAL, MONTREAL,

Frederick T. Merchant, M.D.,

ASSISTANT DEMONSTRATOR IN PATHOLOGY, MC GILL UNIVERSITY,

AND

George B. Maughan, M.D.,

RESIDENT IN OBSTETRICS AND GYNECOLOGY, ROYAL VICTORIA HOSPITAL, MONTREAL, CANADA.

(From the Pathological Institute, McGill University, and the Montreal Maternity Division of the Royal Victoria Hospital.)

In a previous communication[31] the authors have reported changes in the hemoglobin, volume of packed red cells, reticulocytes, and fragility of the erythrocytes in a series of newborn infants over a 9-day period. At the same time investigations were carried out

on the changes in the bilirubin content of the blood plasma, utilizing the Evelyn[7,8] photoelectric colorimeter technique. The present paper is concerned with this phase of our research. Before presenting this, however, we believe it would be advisable to review briefly some of the more pertinent facts in regard to bilirubin and some of the recent advances in our knowledge.

It is now generally accepted that bilirubin and hematoidin are chemically identical and that the hemoglobin liberated from the destruction of red cells is the only known source of bilirubin.[2,24a] The direct and indirect Van den Bergh reactions of bilirubin with the diazo reagent are familiar to everyone, but there has been considerable debate as to the nature of these reactions. Two theories have arisen: 1, that the two types are chemically identical but that in the indirect form the bilirubin is adsorbed by a serum constituent (apparently globulin) and so prevented from reacting directly with the diazo; 2, that there is a difference in chemical composition between the bilirubin normally found in the circulating blood and that which has passed through the liver cells. The experiments of Bollman, Sheard and Mann[3] lent considerable support to the first when they showed that alcohol-acetone and aqueous solutions of serum from cases with obstructive and hemolytic jaundice when measured spectrophotometrically gave similar light transmission curves. Barron[2] demonstrated *in vitro* that direct reacting bilirubin when added to normal serum was transformed into the indirect type, and that the addition of a substance of lower surface tension (which would be more readily adsorbed, thus freeing the bilirubin) such as alcohol, bile salts or cholesterol, brought about a reversal to the original form. The application of this to the function of the liver is apparent. In support of the second theory, Andrewes[1] observed that the direct reacting bilirubin oxidizes more easily than the indirect type. Van den Bergh[30] pointed out that the direct bilirubin is more readily adsorbed by the protein precipitate formed by the addition of alcohol to sera than is the indirect bilirubin, while Grunnenberg[12] found that the direct reacting bilirubin passes into solution with chloroform while the indirect does not. Others have supported one or the other of these concepts, but it is without the scope of this paper to review the literature completely.

With the qualitative and comparatively crude quantitative Van den Bergh methods which have been used in the past, the distinction between the various types of bilirubin reaction was apparently sharp. This led to their usage for diagnostic purposes which, while of distinct clinical value, has unfortunately brought about erroneous conclusions concerning the types of bilirubin as they exist in the blood. This has been well demonstrated by the work of Malloy and Evelyn,[21a] employing the photoelectric colorimeter, which has shown that even in the blood of normal adults from 35 to 70% of

the total bilirubin is the direct type, the remainder being the indirect. By studying the various types of icterus they have found that there are always direct and indirect components of the total bilirubin which exist in varying percentages of the whole, depending upon the pathogenesis of the condition. For example, in jaundice due to biliary obstruction the direct percentage will be 60 to 80% or more of the total, but there will always be a small percentage of the indirect, while in hemolytic jaundice the values for the two forms will be reversed. In other words, the quantitative differences between direct and indirect bilirubin become a more or less relative matter. This would seem to support the view that the differences in relative amounts of the direct and indirect reacting bilirubin material are dependent upon some adsorptive substance which is present in the blood at all times to a slight degree but reaches high figures in the regurgitative (obstructive) types of jaundice.

Icterus neonatorum simplex has been accepted as a normal physiologic process in the readjustment of the infant to extra-uterine life, but there has never been complete unanimity of opinion as to the pathogenesis. Jaundice in the newborn, of course, may be caused by other factors, such as congenital malformations of the bile ducts, sepsis, congenital syphilis, erythroblastosis, and so forth, but we are not primarily concerned here with these. It has been customary in the past to distinguish between icteric and non-icteric infants, although it has been known for some time that all infants show a hyperbilirubinemia at birth, and that this bilirubin reacts indirectly with the diazo reagent.[16,19,23a,29,33] Therefore, the terms icteric and non-icteric refer purely to the objective outward signs of jaundice. The incidence of icterus neonatorum has been variously reported from 30 to 90% or more, according to the criteria laid down for diagnosis.

It is generally agreed that there occurs an increased blood destruction in the newborn which leads to the formation of an excessive amount of bilirubin and which results in a certain degree of hyperbilirubinemia. It is a controversial point, however, in those cases in which the hyperbilirubinemia reaches a level sufficient to cause jaundice, whether this is due primarily to an excessive amount of blood destruction, or whether it is the result of an inability of the liver cells to excrete the bilirubin which has been brought to them, thus resulting in an increasing retention of bilirubin during the first 4 to 7 days of life.

Among the considerations supporting the theory that excessive blood destruction alone is sufficient to explain the jaundice are the observations of Gordon and Kemelhor,[10] Greil,[11] Rolleston and McNee,[25] and others, who found the presence of icterus and the degree of hyperbilirubinemia proportional to the rate of excessive blood destruction as noted by reduction of the red cells and hemoglobin. The hemolytic nature of the icterus was assumed by

Lepehne[17] and others on the basis of the constant indirect reaction of the bilirubin in the absence of the direct reaction. Goldbloom and Gottlieb[9a] attributed the initial polycythemia to the low oxygen tension of the fetal blood, and using guinea pigs showed that increasing the oxygen tension brought about an increased blood destruction and a rise in blood bilirubin. Further, they reported[9b] an increased fragility of the red cells associated with a fall in immature cells. Therefore, from these and the above observations, they concluded that icterus neonatorum was a hemolytic icterus and was the result of a postnatal readjustment from a condition of oxygen unsaturation to one of normal oxygen saturation. Ehrenfest,[5] Schwartz, Baer and Weiser,[28] and others attributed icterus to increased blood destruction on the basis of birth trauma and hemorrhage. Book[4] observed that ligation of the cord before cessation of pulsation reduced the incidence and degree of jaundice, and believed it due to the elimination of about 100 cc. of blood from the circulation. Williamson[32] noted that blood pigment was deposited in the placenta and supported the theory by observing a relationship between icterus and the height of placental iron deposits. Others have lent support to this theory but space does not permit a complete review of the literature.

The second theory, or that of primary liver insufficiency as the essential difference in the icteric and non-icteric infants, has gained considerable support from the observations of McMaster and Rous[20] who showed the normal liver to have a tremendous reserve capacity, so that even a small amount of normal tissue was capable of preventing jaundice in the presence of increased amounts of bilirubin. Rich[24b] doubted if an uncomplicated excessive production of bilirubin was ever the cause of jaundice, and attributed icterus neonatorum to increased bilirubin formation and an impaired function of the liver cells due to immaturity. The physiologic insufficiency of the liver of the newborn was advocated by Yllpo,[33] and Hirsch[16] on the basis of functional immaturity, and they showed by comparative studies of icteric and non-icteric infants that the total excretion of bile pigments in the urine and stool was similar in the two groups, and further, that there was no agreement between the degree of icterus and the total amount of pigment excreted. Hess,[14] Snelling,[29] and Yllpo[33] observed a low initial bilirubin excretion which was followed later by an increased output at a time when the blood bilirubin was falling. Then Ross, Waugh and Malloy[27] showed that in the cases with jaundice the average total excretion of urobilin in the stool and urine was lower than in those without jaundice, which was contrary to what one would expect in a purely hemolytic icterus. On the other hand, it was noted that an appreciable amount of bilirubin was present in the urine of only the icteric group, and they concluded that the liver cells of the jaundiced infants have a temporary functional inability to excrete bile pigment

in sufficient quantity. Levulose tolerance tests by Heynemann[15] and bromsulphonephthalein excretion tests by Herlitz[13] clearly indicated reduced liver function on the part of all infants, as have the observations that jaundice is more frequent in prematures.[18] Snelling[29] advocated liver insufficiency on the basis of interference of normal function by a persistence of hematopoietic activity of the liver which lasted for several days. Elton[6] returned to the original theory of Quincke, to postulate a patent ductus venosus as the cause of the hyperbilirubinemia and jaundice. Grossly, he could find no relationship between blood changes and the intensity of jaundice or the degree of hyperbilirubinemia—a fact which has been mentioned by others.[19,23b,29] Working with dogs, Meier[22] was unable to increase the normal icterus neonatorum by the injection of phenylhydrazine and concluded that insufficiency of the liver rather than blood destruction was the primary factor.

It is apparent, therefore, that there is considerable evidence supporting both the hemolytic and hepatic hypotheses. It would seem, however, if it could be demonstrated by the more precise and detailed methods now available that no relation was found to exist between the amount of blood destruction and the development of icterus neonatorum, then the former theory would have to be set aside. With the material from our studies on newborn infants, it seemed quite possible that this might be done.

Source of Material. The newborn infants studied in this work are the same individuals reported previously[31] and are normal full-term infants born on the wards of the maternity unit of the Royal Victoria Hospital. We limited our study to a 9-day period, making determinations on the day of birth (cord blood), second, fourth, sixth and ninth days. The cord blood was obtained usually after cessation of pulsation in the cord. Thereafter, the blood was obtained from the sagittal sinus by fontanel puncture. The infants were closely observed on the ward in order to detect the occurrence of icterus neonatorum, erythroblastosis, complications and so on. We examined 65 newborns, obtaining complete 5-day studies on 33, 4 out of 5 on 12, and 3 or less on the remainder, with 5 disqualified because of illness or transfer. In all, we carried out over 250 examinations. No attempt is anticipated to follow these infants in the outpatient department.

Technique. Throughout this study we have utilized the Evelyn photoelectric colorimeter[7,8] and a modification of the technique for bilirubin determinations developed by Malloy and Evelyn.[21b] The colorimeter is a stabilized, direct-reading, single photocell, photoelectric colorimeter equipped with light filters. The filter with a maximum transmission of 540 millimicrons was used because light which has passed through it is readily absorbed by solutions of azobilirubin, and further it is unaffected by the yellow serum pigments, the absorption of which is negligible at this transmission. Hemoglobin, of course, as we noted in our first paper, does absorb light through this filter, but any error from this source (unless there is very marked hemolysis) is obviated by the use of a blank tube in the initial adjustment of the instrument. The technique utilizes a high concentration of alcohol (approx. 50%) so that all of the bilirubin reacts with the diazo reagent even in the presence of serum proteins. However, the method eliminates protein precipitation by means of an initial dilution with

water, hence any loss of bilirubin caused by adsorption on the protein precipitate is eliminated. Malloy and Evelyn have been able to recover within 2% of all the bilirubin in serum and other media, and thus the method gives higher and more accurate values than any other method heretofore employed. Our procedure is as follows:

Reagents: 1. Diazo reagent—freshly prepared by adding 0.3 cc. of Ehrlich's solution* No. 2 to 10 cc. of Ehrlich's No. 1. In our modification we used 60% dilutions of the Ehrlich solutions. 2. Diazo blank—9 cc. of concentrated HCl diluted to 1 liter with distilled water. 3. Absolute methyl alcohol.

Procedure: Two colorimeter tubes are set up and into each 5 cc. of a 1 to 20 dilution of plasma is placed. To one tube 1 cc. of the diazo reagent is added, while to the other 1 cc. of the diazo blank is added. The colorimeter is adjusted with the blank tube, then the sample tube is placed in the instrument and read at the end of 10 minutes and again at the end of 30 minutes. The amount of direct bilirubin is then calculated from a prepared table,[21b] the figure from which is divided by 7 to give the final result because of the dilution of our solution. To determine the amount of total bilirubin present in the plasma, 6 cc. of absolute methyl alcohol are then added to each tube and gently mixed. After 15 minutes, the colorimeter is again adjusted with the blank tube, then the sample read. The total bilirubin is then calculated in the same manner as above, but the final result is obtained by dividing by 3.5.

By this method we determine the direct and total bilirubin in plasma, rather than the direct and indirect reacting bilirubin. The difference between the two is, of course, the amount of indirect present. It has been found that an adult will normally have a total bilirubin of 0.2 to 0.8 mg. %, of which about 35 to 70% is of the direct type.

Total Bilirubin. We found the average total bilirubin in the cord blood of 53 infants to be 1.35 mg.% with a dispersion of 0.54 to 1.98 mg.%. The average total bilirubin on the second-day venous blood of 48 infants was 3.17 mg.% (0.33 to 5.94 mg.%), while it was 5.27 mg.% (0.57 to 11 mg.%) in 47 newborns on the fourth day, 4.21 mg.% (0.19 to 13 mg.%) in 41 infants on the sixth day, and 3.1 mg.% (0.32 to 9.3 mg.%) in 41 infants on the ninth day. In our series, 30% of the cases developed icterus neonatorum. Of these 18 infants, all but 5 became jaundiced on the fourth day, the others developing it on the second, third and fifth days (see Table 1).

TABLE 1.—COMPARISON OF TOTAL AND DIRECT BLOOD BILIRUBIN, HEMOGLOBIN, VOLUME OF PACKED RED CELLS, AND INDEX OF FRAGILITY BETWEEN ICTERIC AND NON-ICTERIC INFANTS DURING THE PERIOD STUDIED.

Day.	Total bilirubin, mg. %.		Direct bilirubin, mg. %.		Hemoglobin, gm./100 cc.		Vol. packed red cells, %.		Index of fragility.	
	Icteric.	Non-icteric.	Icteric.	Non-icteric.	Icteric.	Non-icteric.	Icteric.	Non-icteric.	Icteric.	Non-icteric
Cord blood . .	1.39	1.31	0.49	0.53	15.07	15.49	51.1	51.4	390	405
2d day . . .	3.52	2.82	0.51	0.51	15.4	15.54	48.8	49.8	338	350
4th day . . .	6.32	4.22	0.49	0.44	15.3	15.52	47.7	49.2	335	324
6th day . . .	5.67	3.48	0.49	0.53	14.5	15.13	45.1	47.7	346	333
9th day . . .	4.07	2.13	0.53	0.48	14.35	14.85	44.4	46.5	379	344

* Ehrlich's solution No. 1 is prepared by 1 gm. of sulphanilic acid dissolved in 15 cc. concentrated HCl and diluted to 1 liter with water. Ehrlich's solution No. 2 is 0.5% sodium nitrite.

It will be observed that the two groups show the same average total bilirubin in the cord blood, but that the icteric infants have a slightly higher concentration of the pigment on the days examined thereafter. On closer inspection of the individual cases, however, a wide variation in values within the two groups was found. It was noted on the fourth day, when the majority were jaundiced and the values for almost all infants were at a maximum, that of the 15 icteric infants, 12 had a total bilirubin greater than 5 mg.%, while only 3 were less—the lowest being 0.73 mg.%. Of the 32 non-icteric infants, 20 had values less than 5 mg.%, while the remaining 12 showed values greater than this—the highest being 8.1 mg.%.

We feel, therefore, that there is no strict proportion between the presence of visible jaundice and the degree of hyperbilirubinemia, although as would be expected a rough relationship is found and icterus neonatorum for the most part varies only in degree, with 5 mg.% of total bilirubin the approximate threshold for visible jaundice. It should be pointed out that the discrepancies which exist are undoubtedly explained by the frequent difficulty in recognizing slight degrees of jaundice in the presence of racial variations of normal skin coloring and by the differences of opinion on the part of observers. Or, as Ross, Waugh and Malloy[27] suggest, it may be due to a variable affinity of certain tissues in individual infants for bile pigment.

It is interesting to note that all children are apparently born with a quantity of total blood bilirubin which would be regarded as a hyperbilirubinemia in the adult. The cord blood of several prematures was observed to show a similar picture. It seems probable, therefore, that a state of hyperbilirubinemia exists in the fetus at least through the latter months of gestation, and that this state is due to some factor other than the postnatal blood destruction. These cord blood values, however, are low as compared with the hyperbilirubinemia which subsequently develops in the vast majority of the cases.

Direct Bilirubin. We demonstrated a constant quantity of the direct diazo reacting bilirubin during the period studied. The cord blood averages of 51 infants was 0.51 mg.% with a dispersion of 0.06 to 0.94 mg.%. On the second-day venous blood, the average of 48 cases was 0.51 mg.% (0.09 to 1.26 mg.%), while it was 0.46 mg.% (0.13 to 0.79 mg.%) for 47 cases on the fourth day, 0.51 mg.% (0.06 to 1.01 mg.%) for 41 infants on the sixth day, and 0.51 mg.% (0.16 to 0.86 mg.%) for 41 infants on the ninth day (see Table 1). It will be observed that the averages are approximately the same throughout the period for both groups.

The presence of a direct bilirubin reaction in the blood of newborns is contrary to the observations of previous investigators. This is undoubtedly attributable to the method employed, for, as

has been pointed out earlier, similar findings on the presence of a certain amount of direct bilirubin in the blood of normal adults were observed by Malloy and Evelyn. It is apparent from the above data that while there is a marked difference in the quantity of total bilirubin for each day studied and that these amounts are to a certain degree proportional to the presence of clinical jaundice, there is an almost constant amount of direct bilirubin at all times. As a matter of fact, this quantity is much more constant than a glance at the dispersion figures indicates. A survey of the individual cases shows that by far the majority of the infants maintain a value of about 0.5 mg.% during the entire period. In the occasional cases where higher or lower values were recorded, these levels likewise tend to be maintained. It is noteworthy that this constant figure for direct bilirubin in the newborn is distinctly higher than that met with in the normal adult using the same technique. The changes in hyperbilirubinemia are therefore due to variations in the amount of the indirect bilirubin. The findings would all seem to suggest the view that the amount of total bilirubin which has been transformed so as to give the direct reaction is dependent upon the presence in the blood of some substance which is comparatively constant and relatively higher in the newborn infant.

TABLE 2.—COMPARISON OF TOTAL AND DIRECT BLOOD BILIRUBIN, HEMOGLOBIN, VOLUME OF PACKED RED CELLS, AND INDEX OF FRAGILITY AVERAGES BETWEEN ALL CASES DURING THE PERIOD STUDIED. (Number of Cases Averaged Per Day Are Indicated in Parentheses.)

Day.	Total bilirubin, mg. %.	Direct bilirubin, mg. %.	Hemoglobin, gm./100 cc.	Vol. of packed red cells, %.	Index of fragility.
Cord blood . .	1.35	0.51	15.36	51.3	400
	(53)	(51)	(52)	(51)	(52)
2d day . . .	3.17	0.51	15.49	49.5	346
	(48)	(48)	(45)	(45)	(45)
4th day . . .	5.27	0.46	15.46	48.7	328
	(47)	(47)	(46)	(46)	(46)
6th day . . .	4.21	0.51	14.93	46.8	337
	(41)	(41)	(39)	(39)	(39)
9th day . . .	3.10	0.51	14.70	45.9	356
	(41)	(41)	(39)	(39)	(37)

Relation of Total and Direct Bilirubin to Hemoglobin, Volume of Packed Red Cells and Fragility of the Erythrocytes. In Table 2, a comparative study is presented between the average values for direct and total bilirubin, and the findings on hemoglobin, volume of packed red cells, and fragility of the erythrocytes previously reported by us in Part I of this study.[31] It will be observed at once that the total bilirubin values rise to the fourth day after which they fall, while there is a steady decrease after the second day in the averages for hemoglobin and volume of packed red cells. Further, the total bilirubin is highest at the time when the resistance of the red cells, as determined by the fragility index, is greatest. Similar

observations were made on the infants with and without jaundice (see Table 1).

It is apparent, therefore, from the above that hyperbilirubinemia decreases steadily after the fourth day in spite of the fact that there is a continued blood destruction as evidenced by the fall in hemoglobin and volume of packed red cells. It is interesting to observe that as the bilirubin concentration rises, the hemolytic index falls (increased resistance) and conversely, that as the bilirubin falls the index rises. While this might suggest that a change in resistance of the red cells is dependent upon the degree of bilirubinemia, a day-to-day comparison of the variations in the index with the degree of hyperbilirubinemia between icteric and non-icteric infants makes it obvious that no such relation exists. Thus we found on the second-day venous bloods of icteric infants that there was a greater increased resistance and a greater bilirubinemia, while on and after the fourth day the icteric group showed a lessened increased resistance though a still greater bilirubinemia than did the non-icteric infants.

Relation of Hyperbilirubinemia to Blood Destruction. In order to study in detail the relationship between blood destruction and the degree of hyperbilirubinemia, we calculated the fall in hemoglobin for each individual infant during the 9-day study and plotted it against the maximum bilirubin concentration for that infant. Chart 1 indicates that we were unable to demonstrate any relationship between the extent of hemoglobin reduction and the rise in bilirubin. The chart further shows there is no difference in this respect between the icteric and non-icteric infants. A similar chart, not reproduced here, giving the reduction in volume of packed red cells instead of hemoglobin, likewise failed to indicate any direct relationship between the amount of blood destruction and bilirubinemia.

We then constructed scatter charts for each day studied in which the changes in hemoglobin and volume of packed red cells were compared with the amount of total bilirubin on that day. Of these charts, which present an essentially similar picture, that for hemoglobin on the fourth day (Chart 2) only is reproduced here, and it will be found that no relationship exists between the fall in hemoglobin which has occurred since the cord blood determination and the increase in blood bilirubin over the same period.

Furthermore, an attempt was made to demonstrate, if possible, any relationship between the original height of the hemoglobin and the bilirubinemia. For this purpose, the 10 infants having the highest cord blood hemoglobins were compared with the 10 infants with the lowest values. The average fall in hemoglobin in 9 days for the first groups was 1.4 gm., while the average fall for the second group was 0.16 gm. Notwithstanding the marked difference in amount of blood destruction indicated between the two groups, the

average maximum bilirubin of the group with the high initial hemoglobin was 4.59 mg.%, while the average maximum bilirubin for the groups with the low initial hemoglobin was 4.08 mg.%. As will be appreciated, this is a negligible difference and again indicates no relationship between the amount of blood destruction and the degree of bilirubinemia present. A similar finding was obtained using volume of packed red cells instead of hemoglobin.

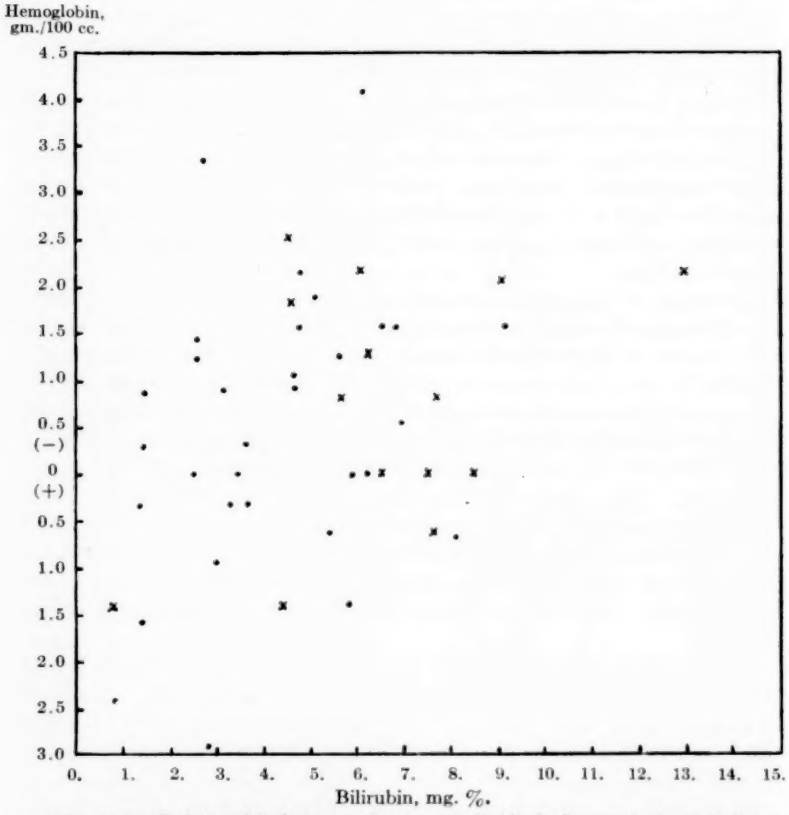

CHART 1.—Relationship between the total individual changes in hemoglobin at the end of the 9 days and the greatest total bilirubin concentration during this period. In this and subsequent charts, icteric infants are indicated with a cross; non-icteric with a dot.

Having failed to demonstrate any relationship between the reduction of hemoglobin and volume of packed red cells and the hyperbilirubinemia, we then took up the question of the hemolytic index for fragility of the red cells to demonstrate whether there was any indication that an infant having a high index of fragility showed a greater bilirubinemia. We plotted in a scatter chart the total

bilirubin on the day it was greatest against the index of hemolysis at that time. This is shown in Chart 3, and it will be observed that no relationship was found to exist either for the icteric or non-icteric infants or the group as a whole.

During the course of our study on normal infants, determinations on several cases of erythroblastosis were carried out. The series is, of course, too small for definite conclusions but the findings are

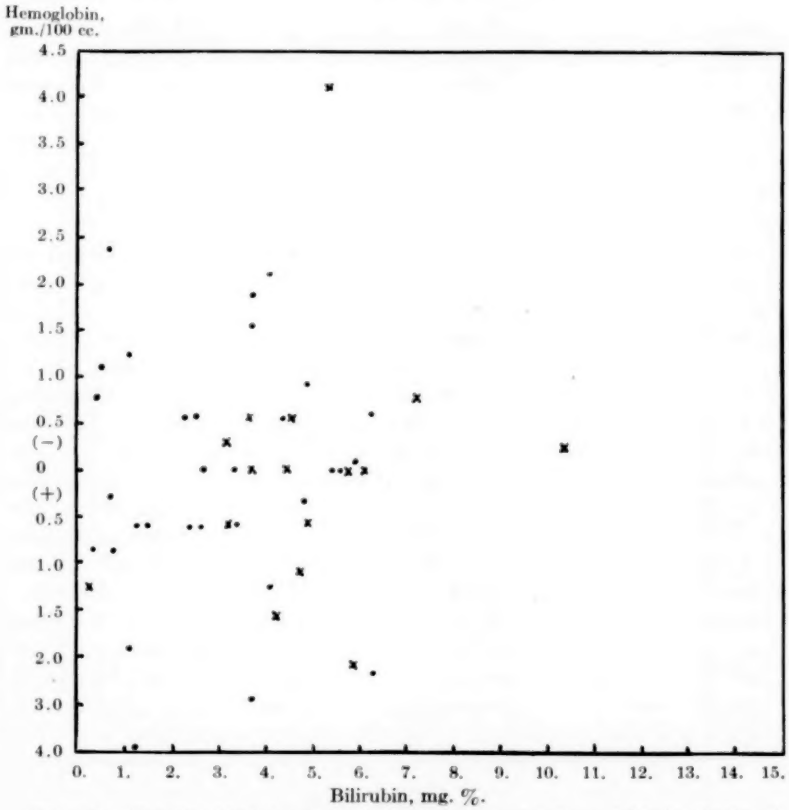

CHART 2.—Relationship between the individual changes in hemoglobin by the fourth day and the total bilirubin rise for the same period.

interesting and seemed worthy of recording here. In these cases the total bilirubin on one cord blood was 3.9 mg.%, one second-day blood was 9.64 mg.%, one third-day blood was 19.4 mg.%, three fourth-day bloods were 18.2, 20.3 and 24 mg.%, and one sixth-day blood was 18.5 mg.%. The direct bilirubin determination for one cord blood was 0.63 mg.%, one second-day blood was 0.65 mg.%, one third-day blood was 1.44 mg.%, three fourth-day bloods were 0.58, 3.12, 3.04 mg.%, and one sixth-day blood was 0.95 mg.%.

It is noteworthy in contrast to the normal infants that children with erythroblastosis are born with a higher total bilirubin but similar direct bilirubinemia. This is in agreement with the clinical evidence that jaundice in these cases is often noted at birth. The total bilirubin then rises rapidly to a much higher figure than met with in the icteric group of normal infants. Moreover, by the third day, the direct bilirubin shows a distinct rise in contrast to the

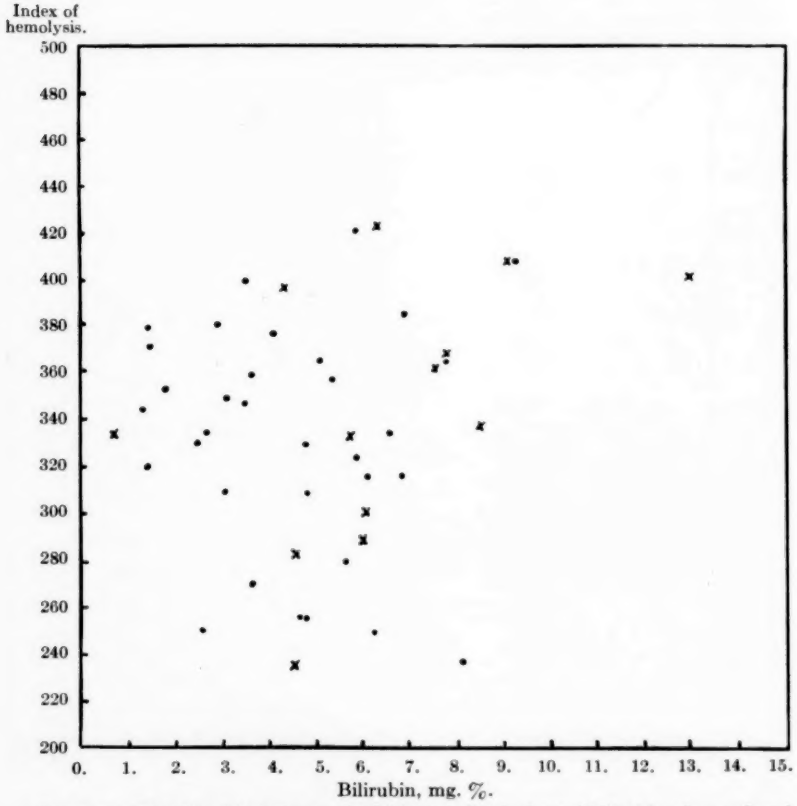

CHART 3.—Relationship between the highest individual total bilirubin observed and the index of hemolysis at that time.

constant figures for the normal infants. This is possibly referable to biliary thrombi often reported in these cases.[26] In Part I of this study we noted in erythroblastosis a distinctly high hemolytic index (increased fragility) for the red cells, and a marked progressive anemia. These infants alone of all those studied showed an increased fragility. There is, therefore, every indication that in this condition we are dealing with a hemolytic form of anemia and by no

means, as some have suggested, simply with an icterus neonatorum of unusually severe degree.

Summary. Our results on 250 bilirubin determinations on newborn infants during the first 9 days of life demonstrate a state of hyperbilirubinemia at birth which increases during the first 4 days, then falls toward normal. Thirty per cent of our cases developed icterus neonatorum. When we compared the presence of clinical icterus with the degree of hyperbilirubinemia, it was found that in a general way icterus was reported when the level of total bilirubin reached 5 mg.% or more. There were cases, however, where icterus was reported with lower blood values, as well as cases where icterus was apparently absent with figures above this level. It would appear all newborn infants are reacting similarly to the readjustments of postnatal life whether they develop clinical jaundice or not.

We have attempted with the material at our disposal to determine the existence of any relationship between the amount of blood destruction taking place during the first few days of life and the degree of hyperbilirubinemia and the development of icterus neonatorum. For this purpose we have shown: (1) that there is a continuous fall in hemoglobin and volume of packed red cells throughout the period studied, while the bilirubinemia reaches it greatest level on or about the fourth day and then declines toward normal; (2) that no relationship exists either between the individual total fall in hemoglobin and volume of packed red cells and the amount of bilirubinemia during the 9 days studied or between the changes in hemoglobin and volume of packed red cells and the total bilirubin concentration on any particular day; (3) that there is no relationship between the original height of the hemoglobin and the volume of packed red cells, and the development of hyperbilirubinemia. Further, as was noted in Part I of this study, no correlation could be demonstrated between the original height or subsequent changes in the individual values for hemoglobin and packed red cells and the appearance of clinical jaundice. (4) We have clearly shown the resistance of the erythrocytes to be increased during the period studied, and that variations in the index of hemolysis in normal infants have no effect upon the degree of hyperbilirubinemia which develops. (5) In our various studies on the relationship of blood destruction and fragility of the erythrocytes to the degree of bilirubinemia, no significant differences could be found to exist between the icteric and the non-icteric infants. These findings all refute the conclusions of those who have supported the hypothesis that the development of icterus neonatorum is dependent upon the amount of blood destruction or the presence of an abnormal hemolytic condition in the blood at the time of birth. It is, of course, quite apparent that the presence of an increased blood destruction allows for the production of a large amount of bilirubin in a comparatively short time and makes possible the development of an

excessive amount of blood bilirubin. However, neither the height of the bilirubinemia nor the consequent development of icterus neonatorum bears any direct relation to the amount of blood destruction in the individual case.

There is nothing in our findings which contradicts the views of those who explain the development of jaundice on the basis of variations in the ability of the liver cells to excrete the excessive bilirubin transported to them at this time. While our observations do not prove the hepatogenic theory, their lack of any contradiction offers strong support for it, especially when taken into consideration with the literature briefly reviewed earlier. We are, therefore, of the view that hyperbilirubinemia in general and icterus neonatorum in particular are made possible by the increased blood destruction which is obviously taking place during the first few days of life, but, that whether the infant develops a sufficient bilirubinemia to exhibit clinical icterus is dependent upon the functional ability of the liver cells to excrete it.

The methods employed have allowed for a quantitative analysis of the amount of bilirubin giving the direct and indirect reactions. It has been demonstrated that the hyperbilirubinemia in the normal infant during this period, whether it reaches a level sufficient to produce icterus or not, is due entirely to a rise in the indirect bilirubin, while the direct bilirubin maintains an extraordinarily constant level.

In the few cases of hemolytic anemia of the newborn (erythroblastosis) which came under our observation, it was demonstrated that these infants are born with a hyperbilirubinemia which reaches a much higher figure than in the normal infant, whether jaundiced or not. Moreover, while the direct bilirubin was not increased as compared with the normal infant at birth, it likewise tended later to rise, suggesting the development in these cases of an associated obstructive factor. At the same time it was observed that these cases showed an increased fragility of the red cells and a severe anemia as compared with the normal infants. This we believe is indicative of a different process from that which is taking place in icterus neonatorum.

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THE DOUBLE QUOTIDIAN TEMPERATURE CURVE OF GONOCOCCAL ENDOCARDITIS. A DIAGNOSTIC AID.

By Palmer Howard Futcher, M.D.,

ASSISTANT RESIDENT PHYSICIAN, THE JOHNS HOPKINS HOSPITAL; ASSISTANT IN MEDICINE, THE JOHNS HOPKINS SCHOOL OF MEDICINE, BALTIMORE, MD.

(From the Medical Clinic, the School of Medicine, Johns Hopkins Hospital and University.)

In his monograph on septicemia, Lenhartz[7a] described the usually constantly elevated, weakly remitting temperature curves of staphylococcal and pneumococcal bacteremia, the irregularly intermittent curves of streptococcal and colon bacillus bacteremias, and the somewhat similar, high, intermittent fever accompanied by frequent shaking chills seen in gonococcal sepsis. Other authors have been struck by the highly regular, often quotidian variations in the fever of gonococcemia,[3,8] and the temperature curves seen in gonococcal endocarditis have been subdivided into those: *a*, continuous with remissions; *b*, essentially intermittent; and, *c*, intermittent and remittent.[10,12] While it is thus general knowledge that, as a rule, in gonococcal endocarditis the oscillations in the fever through the 24 hours are greater and at the same time often more uniform from day to day than in other forms of bacterial endocarditis, there is no general recognition of one particular form of temperature curve which would seem relatively specific for gonococcal endocarditis. This special temperature curve is the subject of this paper.

Horder,[3] in 1909, writing on general aspects of bacterial endocarditis, presented temperature charts of 2 patients stated to have gonococcal endocarditis; each chart showed *two* peaks of temperature each day, one in the morning and one in the evening, for a period of several days, with a rapid fall to normal or subnormal levels following each peak. He also referred to a somewhat similar chart of a case reported by other authors[2] and stated that double

quotidian intermittent fever was common in gonococcal endocarditis. More recently, Horder and Gow[4] commented that the appearance of 2 spikes in 24 hours on a temperature chart suggests gonococcal septicemia or kala-azar. Lenhartz,[7b] even earlier than Horder, described a patient with probable gonococcal endocarditis and presented a temperature chart which he characterized as "intermittens quotidiana duplicata." Other authors writing on gonococcal endocarditis have described similar temperature curves in individual cases, either without any significant comment whatever in the text,[5,6,11] or, like Lenhartz, with merely a note on the peculiarity of the curve in the particular case (Harris and Johnston,[2] Oettinger, Marie and Morancé,[9] and Thayer[12]). The only writer other than Horder and Gow to note that this temperature curve is character-

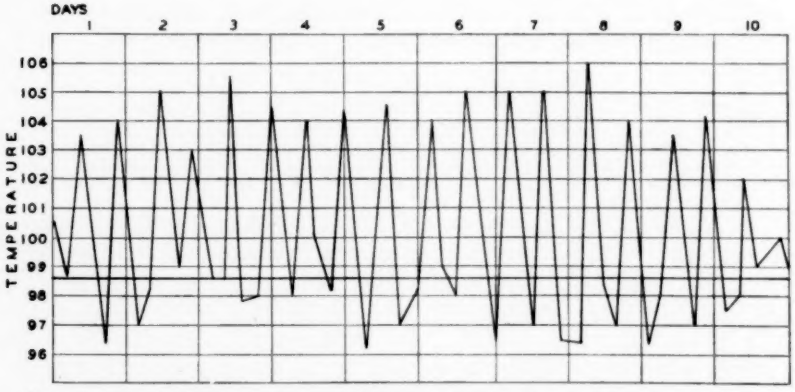

FIG. 1.—THE DOUBLE QUOTIDIAN TEMPERATURE CURVE OF GONOCOCCAL ENDOCARDITIS WITH TERMINATION OF THE CYCLE AFTER 10 DAYS.

L.S., M4891, a white female aged 34 years, admitted April 25, 1895, died May 16, 1895. The gonococcus was cultured from the blood during life. Autopsy revealed that the endocarditis involved the mitral valve.

istic of gonococcal endocarditis was R. H. Williams,[13] who, in commenting on the great frequency of chills in this disease, emphasized that almost daily "double peaks" occurred on the temperature charts of 6 of his 12 patients. It was during our association with Dr. Williams in 1938 that, when the diagnosis was still in doubt, he pointed out the significance of the double peaks on the chart of a patient with a cardiac murmur subsequently demonstrated to have gonococcal septicemia (reported elsewhere[1]); thereby he stimulated us to determine the incidence of the phenomenon in the patients with gonococcal endocarditis observed at the Johns Hopkins Hospital.

The temperature charts of 24 patients with gonococcal endocarditis were examined. The diagnosis was established by postmortem examination in 22. Of these autopsied cases in, 12 blood

cultures made during life were positive for the gonococcus; in 2 others there were positive cultures from the endocardial vegetation after death; and in the remaining 8 cases, Gram-negative diplococci were found in the smears made from the vegetations, though they could not be cultivated. Of the 2 cases not autopsied, 1 had a blood culture positive for the gonococcus before death, postmortem examination being refused; another patient, whose blood culture was also positive, recovered from her illness.[1] All of these 24 patients were in the hospital for 6 days or longer; we did not examine the records of several other patients who were on the wards for only 1 to 3 days, since the temperature charts on these patients were too brief to be evaluated.

Ten of the 24 charts showed the double peaks for a period of from 5 to 22 consecutive days, averaging 10 days. An eleventh chart had shown the double peaks for one day when, on the second day following admission, the patient was treated with sulphanilamide with a consequent modification of the temperature curve. Thus 11 of the 24 patients (46%) showed the double peaks.

The prototype of these 11 patients is one who, at 6 A.M., has a shaking chill lasting a few minutes followed by a rise in rectal temperature from an initial level at 4 A.M. of 98° to 105° at 8 A.M., with subsequent sweating and a precipitous fall to 98° at 4 P.M. Then follows repetition of the chill and the rest of the episode at 6 P.M., and the temperature returns to 98° by 4 A.M. of the next day only to renew the 12-hour cycle. There was moderate variation in the timing of the episodes from day to day in the same patient. Thus the chill may come at 8 o'clock instead of 6 o'clock; 1 patient temporarily had peaks at noon and midnight, the fever subsequently returning to the more common morning and late afternoon elevations. For a period of several days the interval occupied by the cycles may be 10 or even 8 hours, with two and a half to three cycles a day. It is very common for an occasional cycle in the series to be abortive, or for one cycle to last longer than the usual 12 hours, so that there may be only one peak during the course of 24 hours, with reversion to the 12-hour cycle the next day. Thus in our series of 11 cases a total of 184 peaks were observed in 103 days. The chills also may vary markedly in intensity from day to day. Usually the fever is intermittent, falling below 98.6°, and not infrequently to 97° or 96°, after the fastigium. In 1 patient, however, the fever was constantly sustained, with the superimposed double quotidian variation producing a regularly remittent character. These cycles we describe are not due to the administration of antipyretics, which were withheld in most of the cases. They were best demonstrated by taking the patient's temperature every 2 hours. Some patients were prostrated by their disease; others suffered it with a remarkable temporary appearance of well-being.

It should be emphasized that the charts described did not show

the double-peaked temperature curve during the whole period that the patient was observed, or even during the majority of it. Usually a patient with a previously intermittent curve lapsed temporarily into the 12-hour cycles for a period of 1 to 3 weeks, the curve subsequently becoming irregular again. Only 2 moribund patients ran the cycle with any regularity; a tendency to flattening and lowering of the temperature curve terminally in endocarditis has already been commented on by Horder[3] and Thayer.[12] The cycles were commonly present at any time from early in the disease until the last week. On more than one occasion a patient at the time of admission related that he had been subject to 2 chills daily since his symptoms had begun. All of the 4 patients with gonococcal endocarditis which have been treated with sulphanilamide at this hospital were running the double quotidian fever when the drug was first administered; the double peak disappeared within 48 hours, and there was subsequent lowering of the temperature curve in all of them. The phenomenon therefore will probably not be observed in patients receiving sulphanilamide.

The occurrence of the usual 12-hour cycles could not be correlated with any particular valve involved by the gonococcal vegetation; the pulmonic, mitral or aortic valves were involved in our 11 patients with no significantly predominant site. There was no correlation with the duration of the course of the disease or with the stage of the illness at which the patient was observed, save that, as already noted, the cycles were uncommon in the last week of life.

In the patients who never showed the cycles, or in those who were not showing them for the time being, the fever was usually high and intermittent, often with a regular 24-hour cycle and diurnal variations from 5° to 7°; slightly less commonly the fever was remittent, and frequently the curve was intermittent at one period of the disease and remittent at another.

The charts of 3 patients with gonococcal septicemia uncomplicated by endocarditis were examined. None of the 3 showed sustained double peaks, although 2 of them showed an irregular, double quotidian curve for 48 hours.

A small series of 13 charts of patients who had been demonstrated at autopsy to have an endocarditis due to the beta hemolytic streptococcus was examined; the patients had died before the advent of sulphanilamide and hence their course was uninfluenced by that drug. It was thought that, since hemolytic streptococcal septicemia often produced high, intermittent fever, the double peak phenomenon might also be present in that type of endocarditis. Two of the 13 charts did show a suggestion of double quotidian fever, but in these 2 cases the curve was remittent rather than intermittent, the swings were of only 1° or 2°, and the cycle was never consecutively repeated for more than 48 hours. Thus neither

these charts, nor those of streptococcal septicemia presented by Lenhartz,[7a] were really similar to those of gonococcal endocarditis which we have described above. Recently there came to autopsy 2 patients who for 3 and 7 days respectively ran remittent fevers with irregular double peaks. One patient had an anaërobic gamma hemolytic streptococcal septicemia secondary to an infected abortion, and the other a pylephlebitis due to a staphylococcus and an unidentified Gram-negative bacillus.

The explanation for the 12-hour febrile cycle in gonococcal endocarditis is not apparent to us. We merely emphasize the phenomenon as a valuable aid to diagnosis in those cases in which it occurs, feeling that it deserves somewhat more prominence than is assigned to it in the papers already cited.

Summary. A study of the temperature charts of 24 patients suffering from gonococcal endocarditis showed that in 11 there was a striking double quotidian variation in fever lasting over a period of from 5 to 22 days.

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RÔLE OF THE "STATIC BLOOD PRESSURE" IN ABNORMAL INCREMENTS OF VENOUS PRESSURE, ESPECIALLY IN HEART FAILURE.

I. THEORETICAL STUDIES ON AN IMPROVED CIRCULATION SCHEMA WHOSE PUMPS OBEY STARLING'S LAW OF THE HEART.

By ISAAC STARR, M.D.,
HARTZELL PROFESSOR OF RESEARCH THERAPEUTICS,
AND
ARTHUR J. RAWSON, M.E.,
ASSOCIATE IN MEDICAL PHYSICS, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

GENERALIZED congestion of the veins has always been a symptom on which clinicians have laid much stress. Occurring so often late in the course of chronic cardiac disease, it has generally been inter-

preted as indicating incompetence of the heart muscle. The idea that "back pressure" caused venous congestion when the heart weakened followed the recognition of mitral stenosis. The analogy between venous congestion and the effect of a dam on a stream of water was put forward at that time.[8]

The experimental era dates from Cohnheim,[2] who injected fluid into the pericardium of dogs to handicap the heart. In these experiments the venous pressure rose and so this venous congestion was attributed to cardiac weakness. However, the arterial pressure fell in Cohnheim's experiment; that this did not occur in clinical congestive heart failure was unknown to this author for it was not discovered until 1905. Therefore these experiments did not produce a condition analogous to clinical congestive heart failure, as was then believed. Analogies between clinical congestive failure and the behavior of a simple circulation schema were emphasized by Starling as early as 1897.[13a]

Because of these and many other observations a view of the mechanism of congestive failure was evolved which was so widely accepted by clinicians that we shall call it the classic view.[13a] It may be summarized as follows. The primary cause is believed to be weakness of the heart muscle. Compensated for a time by hypertrophy and dilatation, eventually increasing weakness results in a diminished cardiac output which initiates two trains of events. First, as a metabolic consequence of the slow circulation, the oxygen supply to the body's tissues is reduced, their normal metabolism is interfered with, and a characteristic train of symptoms results. Second, as a *mechanical* consequence of the diminished circulation, blood accumulates in the veins, produces passive congestion of organs, raises the venous pressure, and so leads to another familiar train of symptoms. This view was generally accepted before measurement of cardiac output was possible.

The results of estimations of cardiac output in congestive failure have led some authors to question the correctness of the classic viewpoint.[7] All agree that the average cardiac output found in congestive failure is smaller than the average found in normal persons. But when the results obtained in individual cases are considered there is evidence that many cases of congestive failure have a higher cardiac output than many persons without this complication, that the severity of the symptoms has no invariable relation to the output, and that improvement is not always accompanied by increase in output. So certain authors believe that reduced cardiac output is no essential part of congestive heart failure.[7]

In the face of these facts several courses are open to students of the subject. The classic view may still be supported.[4,7] The averages of all the cardiac output results, and the results obtained in some patients, are consistent with this view. The discordant results are only found in some individuals and, as cardiac output methods

are not highly accurate, chance accumulation of errors would account for some of the discrepancies.[9] Although the most careful experimenters have employed special precautions to safeguard their results, the extra difficulties inherent in estimating cardiac output when the lungs are congested are generally recognized. We are aware of a number of investigators who, after attempting to estimate cardiac output in congestive failure, decided that it could not be done with enough accuracy to make the effort worth while.

Other authors, accepting the cardiac output results as inconsistent with the classic view, have modified their ideas of the mechanism of congestive failure. Thus Altschule[1] points out that the cases of congestive failure with normal cardiac outputs have abnormally high metabolic rates. He believes that congestive failure occurs because the supply of oxygen and other metabolites is insufficient to meet the tissue demand, not because cardiac output diminishes below a certain level. This concept reconciles the cardiac output results with one part of the classic viewpoint, but it throws no light on the mechanism of the venous congestion in this condition. According to Harrison's view,[7] venous congestion with a normal cardiac output may be attributed to a weakness of one side of the heart relative to the other, the blood accumulating before the weaker heart. McMichael[10] thinks of the congestive phenomena as being a mechanism by which the body compensates for cardiac weakness, not as a mechanical consequence of a diminished circulation.

Our interest began with the discovery that certain patients with small hearts had abnormally small cardiac outputs relative to the size of their bodies.[16] According to the classic view one would have expected venous congestion. But none was present, and in the 5 years that have elapsed none has developed in the cases followed. This observation indicated clearly that venous congestion was no necessary mechanical consequence of a diminished circulation, and led to a decision to investigate the other factors which might bring it about.

Reviewing the literature we found the view that venous congestion was directly caused by cardiac weakness to be supported by mechanical analogies of a very crude sort, like the effect of a dam on a flowing stream and the behavior of circulation schemata with mechanical pumps which, unlike the heart, sucked fluid from the "veins." The failure to reproduce this feature prevented any adequate simulation of the double mammalian circulation with two pumps.

Our plan was to construct a circulation schema which behaved in a more physiological manner than its many predecessors; and, having ascertained the causes of venous congestion when one or both sides of its "heart" were weakened, to undertake a similar analysis in the clinic which, we hoped, might throw light on some of the per-

plexing problems of "congestive heart failure." Preliminary reports on this work have already been published.[14,15]

Accordingly we constructed a two circuit schema whose pumps obeyed Starling's "Law of the Heart," and its behavior made us see the problems of venous congestion in a new light. This experience forms the subject of this paper. In a second paper the clinical research, suggested by the behavior of our schema, is recorded.

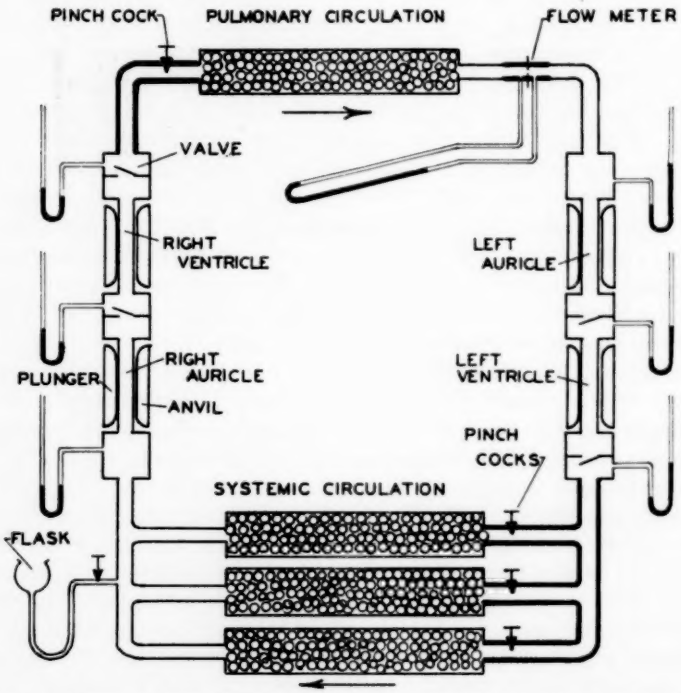

FIG. 1.—GENERAL ARRANGEMENT OF SCHEMA. Arterial portions, made from thick walled rubber pressure tubing, are shown by heavy lines. Venous portions, made from very flexible drainage tubing, are shown by light lines. Capillary beds are made from large Gouch tubing, filled with glass beads. Manometers are connected through short lengths of glass capillary (not shown) to damp oscillations. The flow meter is a thin plate inserted in a short length of metal tube. The diameter of the orifice in the plate is approximately one-half the inside diameter of the tube. Pressure taps immediately above and below the plate lead to a sloping tube manometer.

Apparatus. The schema has about one-tenth the "blood volume" and "cardiac output" of a normal man. The "heart" rate can be varied from 50 to 150 per minute.

The plan and details of construction can be seen from Figures 1 and 2. The cams were designed from data in Wiggers' book,[19] and, although the cam follower did not always follow the cam at high speeds, optical records showed that the arterial pressure curves approximated those obtained in experiments on animals.

Excursion of the mercury manometers was damped by the use of short lengths of 1 mm. bore glass tubing, as only mean pressures concerned us.

At first, in order to mimic blood viscosity, the system was filled with 30% sugar solution (sp. gr. = 1.127). In the later experiments, water was used without any noteworthy change in results.

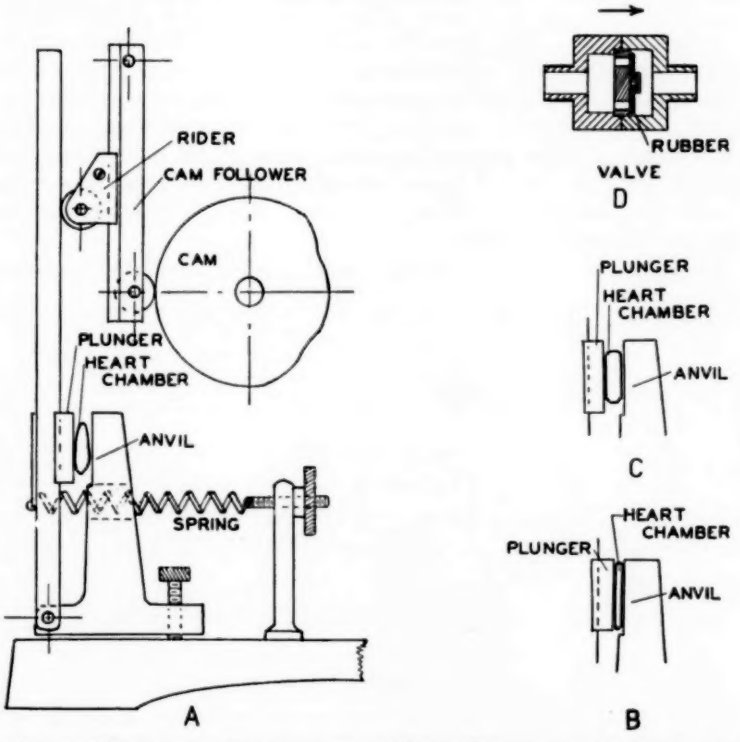

FIG. 2.—MECHANICAL ARRANGEMENT OF HEART CHAMBERS. A ¼ H. P. shunt motor (Janette Mfg. Co., Chicago, Ill., Type 1–DS–16) with two built-in 16 to 1 reduction gears, drives four cams, one for each chamber. The motor speed is controlled by field and armature rheostats.

A. Heart chamber is contracted by spring pulling plunger towards anvil. Heart chamber is relaxed by cam acting through cam follower and rider. Moving rider along cam follower varies length of stroke of plunger. Heart chamber is shown relaxed and only partly filled, as occurs with low venous pressure.

B. Heart chamber contracted.

C. Heart chamber relaxed and completely filled as occurs with high venous pressure.

D. Detail of valve. Soft rubber disk seats against perforated metal disk.

The flow meter was calibrated by opening the system and allowing the pumps to pump from a reservoir into a container. The differential manometer could be read to 1 mm., the arms having a difference of 4 cm. at the highest flows used. At low flows a considerable error was involved, some of the points obtained deviating from the ideal calibration curve by 10%.

"Heart" work has been approximated by the formula: work = flow × pressure, the figure employed for pressure being the difference between the mean pressures of the damped arterial and venous manometers. Thus the

velocity factor and the component of work utilized within the heart were not estimated.

Resistances were calculated from the formula $R = \frac{\text{Pressure drop}}{\text{Flow}}$.

Before each experiment the resistances were adjusted to give physiological pressures throughout the system and the ventricular springs were set so that the work of the right "heart" equaled about one-third that of the left.

Experimental. *The Properties of the Schema.* Starling's experiments[11] involving the measurement of the heart's work and volume could not be duplicated on our schema due to difficulties in measurement of the "heart's" volume. Therefore we contented ourselves with measuring the relation between "venous" filling pressure and the "heart's" work. It seems obvious that the "heart's" volume would be dependent on filling pressure at any constant heart rate. Figure 3 shows the results.

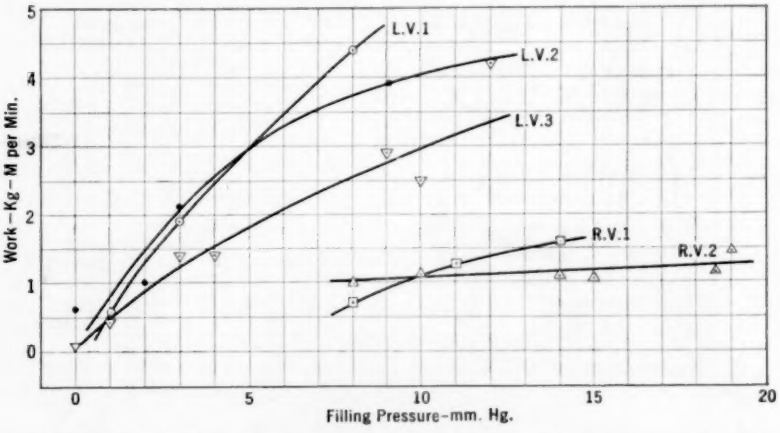

FIG. 3.—Curves illustrating the relationships between filling pressure and work in the pumps of our schema. In R.V.2 cardiac failure has been simulated by weakening the spring. The other curves show the response to increased filling when strength is intact.

The simulation of Starling's "Law of the Heart"[13b] is brought about by the schema as follows: As the "heart" fills, the band tubing changes its shape; flattened when empty, it becomes more cylindrical as it is filled. During "systole" the spring's force is exerted partly on the fluid and partly against the cam. The fuller the "heart," the greater is the proportion of the spring's force expended on driving the fluid, and the less the proportion lost in pressing against the cam. So increased filling leads to a greater output of work by the pump.

If the spring is weakened beyond a certain point, all its power is applied to the fluid and none to the cam. Under these conditions increased filling no longer causes increased work, an analogy to what is found in physiologic heart failure.[11] Curve R.V.2 (Fig. 3) illustrated this point.

The Definition and Measurement of Static Blood Pressures. Our studies emphasize the great importance of the pressure existing throughout the "vascular" system when the pumps are stopped. This static pressure is named the *mean systemic pressure* in Starling's textbook.[13c] The term is introduced in a discussion of a simple schema with a single pump. Applied to our schema, or to the mammalian circulation, the term chosen by Starling is confusing as it suggests the mean of the arterial, capillary, and venous pressures in the systemic circulation during heart action. Therefore we propose to avoid a term so likely to be misunderstood and to call this property of any fluid system, the pressure which persists throughout the entire circulation after cardiac action has stopped, the *general static pressure.**

TABLE 1.—THE EFFECT OF WEAKENING ONE OR BOTH SIDES OF THE SCHEMA'S "HEART."

	Static pressures measured with circulation stopped.			Pressures measured during circulation.					Heart work.			
	All vessels open.	Great veins clamped.		Systemic		Pulmonary.						
Exp. No.	General static pressure (mm. Hg).	Systemic pressure (mm. Hg).	Pulmonary pressure (mm. Hg).	Arterial (mm. Hg).	Venous (mm. Hg).	Arterial (mm. Hg).	Venous (mm. Hg).	Cardiac output (cc/min.)	Left (gm. meters per min.).	Right (gm. meters per min.).	Heart rate (per min.).	Remarks.
1A	13	11	15	95	5	26	8	172	203	49	90	Initial readings
B	13	12	16	65	8	21	9	120	92	21	90	Both hearts weakened
C	13	12	16	95	6	24	12	87	98	21	90	Systemic resistance increased by tightening screw clamps
D	34	31	40	93	27	49	34	172	138	51	90	Clamps as in A and B. Fluid added to circulation
2A	13	13	18	90	7	30	13	198	152	46	72	Initial readings
B	13	14	10	65	12	14	6	122	98	3	72	Right ventricle out
C	27	30	22	105	27	27	14	158	196	..	72	Fluid added
3A	13	12	20	79	8	32	10	174	163	57	90	Initial readings
B	13	11	21	45	5	35	19	100	35	41	90	Left ventricle weakened

The general static pressure was always measured with the "heart" stopped in both "systole" and "diastole"; the figures given in Table 1 are the averages of the values obtained. Care was always necessary to ascertain whether any manipulation of the schema, such as weakening a "heart" or changing a resistance, altered the static pressures.

* In a preliminary report we called this pressure the "non-cardiac pressure." We later found that the term "static pressure" had been employed previously by Bolton. The use of the older term seems preferable to the introduction of a new one.

If such alteration was found it was corrected by adding or withdrawing small amounts of fluid from the system.

In some experiments we studied the volume of fluid and the static pressures in both the "systemic" and "pulmonary" circuits. With the circulation flowing, hemostats were placed simultaneously on both great "veins," and then the pumps were stopped immediately. This maneuver was repeated at least four times to guard against occasional failure to obstruct the "veins" simultaneously. After equilibrium within each circuit had occurred, pressures were measured with the "hearts" stationary in both systole and diastole, the averages giving the "*pulmonary*" and the "*systemic*" *static pressures* respectively.

Results and Discussion. The results of certain important experiments have been recorded in Tables 1 and 2.

Effect of Weakening One Side of the Heart. As soon as one "heart" is substantially weakened the other "heart" is not filled so full and accordingly, although its strength is intact, the work it performs on the circulation is reduced. The magnitude of this effect depends on the general static blood pressure. Thus, if this pressure is low, weakening the right "heart" has a far greater effect on the left "heart's" work than if this pressure is high (Table 2).

TABLE 2.—EFFECT OF COMPLETE FAILURE OF "RIGHT VENTRICLE" AT DIFFERENT LEVELS OF GENERAL STATIC BLOOD PRESSURE.

(Ratio of "right heart" to "left heart" work before failure = 1:2.3 in each exp.)

General static blood pressure (mm. Hg).	"Cardiac output" after failure of R. V. in % of its value while R. V. was normal.	Left "heart" work after failure of R. V. in % of its value when R. V. was normal.
7	42.5	22
13	55	65
21	60	68

Increased Static Blood Pressure as a Means of Compensation for Heart Failure. If fluid is added to the circulation, the static pressure is increased, and cardiac output and work increase also. In this respect the schema behaves like the closed circuit heart-lung preparation of Daly.[3] In the same manner increased static pressure can partly or completely compensate for weakness of one or both sides of the "heart." Table 1 gives typical examples of these effects. But it should be pointed out that while the diminution of flow resulting from complete failure of the weaker right "heart" can be restored by an increased static pressure, only partial failure of the stronger left "heart" can be compensated by this means.

Hydraulic Principles Concerned in Failure of the Circulation. The behavior of a simple schema with tubes of uniform elasticity and a single pump is well described by Starling.[13a,c] With the pump at rest the general static pressure read from a manometer open to the air, indicates the terms of equilibrium with the environment. Start the pump, the internal pressure at one point remains at the

static pressure, fluid accumulates on the arterial and diminishes on the venous side of this point; and the pressure on the "arterial" side becomes higher, on the "venous" side lower than the static pressure. Slow the circulation and both "arterial" and "venous" pressures approach the static pressure as fluid leaves the arteries and accumulates in the veins. Thus weakening the heart causes an increase of "venous" pressure.

Our schema has two pumps, and two sides of the circulation, so additional factors enter into its behavior. When the left "heart" is weakened, without altering the clamps controlling the resistance (Table 1, Exp. 3), fluid accumulates in the "pulmonary" side and diminishes in the "systemic"side. If the circulation is now stopped by the simultaneous clamping of both great "veins" as described on page 33, the static pressure is higher in the "pulmonary" than in the "systemic" side. Therefore the behavior of our schema is controlled by the principles described by Starling for a simple schema, superimposed on its ability to shift fluid from one side to the other.

Factors Concerned in Elevating the Venous Pressure. With these fundamental principles in mind, the hydraulic factors which control venous pressure may be analyzed by dividing them into three groups.

Group 1 contains the factors which control the distribution of fluid between the arteries, capillaries and veins on each side.

Group 2 contains factors which control the distribution of fluid between the systemic and pulmonary circuits.

Groups 3 contains the factors which change general static blood pressure and so alter pressures all around the circulation, the change appearing most conspicuously where pressures are lowest, *i. e.*, in the veins. Such an increase of venous pressure may be brought about by the introduction of fluid within the elastic vessels, by increased tension exerted by the vessel walls themselves as in widespread vasoconstriction, and by increasing the external pressure on the fluid-containing vessels as when edema stretches the skin. In our schema a given increment of static pressure causes a smaller increment of "venous" pressure. This is because the "heart" is stimulated as its filling pressure increases, the circulating is accelerated, and the factors of Group 1 antagonize those of Group 3. So the ability of the heart to respond affects the net result.

If any increase of venous pressure found in the clinic, could be analyzed to find which of these factors predominated, much insight into its etiology and significance would be gained. In the paper which follows this we have attempted such an analysis and the results are to be found therein. But in the clinical literature a rise in venous pressure is frequently explained by other analogies and two must be described in detail as our schema demonstrates certain aspects of the hydraulics which have not always been fully appreciated.

The Dam and Stream Analogy. Following many examples in the older literature, Wenckebach[18] likens the rise in venous pressure after cardiac weakness to the rise of pressure upstream from a dam constructed in a river. If one obstructs a river by building a dam, pressure upstream rises until the flow over the dam equals the inflow. The dam has no effect on the source of power upstream and so no lasting effect on the flow.

The situation in our schema after partial obstruction of the "vena cava," or after weakening the "heart," is very different. As soon as such an obstruction is established the right "heart" does not fill so full, therefore its output is reduced and this affects the left "heart" similarly. Therefore, unlike the river and dam, both pressure and flow are affected. If the "vessels" are quite rigid there is a good rise of pressure above the obstruction although flow is reduced also. But if the "vessels" upstream from the point of obstruction are easily distensible, flow will be affected much and pressure little if at all. Under similar conditions profound weakening of the right "heart" will likewise have almost no effect on "venous" pressure. The dam and stream analogy gives a false impression of simplicity to a physiologic situation which is in reality much more complex.

Back-pressure. An old clinical school of thought attributes the increased venous pressure of congestive heart failure to back-pressure from a weakened heart. The following example, a shortened form of that given by Harrison,[7] gives the mechanism of the rise of venous pressure according to this viewpoint. The left ventricle is expelling 40 cc. per beat. It weakens and then expels only 39 cc. For a short period the inflow into the left ventricle will continue to be 40 cc., and so, for a time, it receives more blood than it expels and slowly becomes dilated. While it is stretching, its internal diastolic pressure will rise, and, first the auricle, and finally the veins, will likewise receive more blood than is expelled from them, the pressure within them rising as their volume increases. This rising venous pressure increases the filling of the ventricle until its fibers, being more stretched, contract more strongly according to Starling's Law of the Heart. Therefore eventually the ventricle expels 40 cc. once more, as much as it receives. Equilibrium is now reëstablished with the same cardiac output, the same arterial pressure, a larger diastolic heart size, and a higher venous pressure than before.

In our schema we have tried to reproduce this sequence of events by weakening one or both sides of the heart, but entirely without success. Diminution of flow and arterial pressure always accompanied the rise of venous pressure after the heart had been weakened. Reflecting on this failure we were forced to the conclusion that, while we could not deny that the changes described in Harrison's example might properly portray a train of events which may occur in clinical congestive failure, one could not regard cardiac weakness

as the direct mechanical cause of this train of events without invoking a mechanism inconsistent with the second law of thermodynamics. According to the examples cited, at the final equilibrium, the energy content of the circulation is higher than it was at the beginning; for venous pressure has risen and all else is the same as before. This *increase* in total energy cannot be the mechanical result of a temporary *decrease* of the energy imparted to the system by the heart.

Analysis of the Increased Venous Pressure When Congestive Heart Failure is Simulated in the Schema. When other factors were unaltered proportional weakening of both sides of the "heart" caused a rise of both "venous" pressures, a concomitant fall of both "arterial" pressures, and a diminished flow (Table 1). The pressure relations of congestive heart failure, increased systemic venous and normal systemic arterial pressure, cannot be reproduced by simply weakening the "heart" (Table 1, 1A and B) and this picture must be brought about by another or at any rate an additional mechanism. To discover it we first weakened the "heart" and then attempted by three separate maneuvers to restore "systemic arterial" pressure and so to reproduce the pressure relationships found in clinical congestive failure.

First, the pinchcocks on the "systemic" arteries were tightened. The "systemic arterial" pressure rose to normal, but "systemic venous" pressure fell back almost to its normal level, and flow was diminished still further (Table 1, 1C). So, clinical heart failure was still not simulated.

In a second attempt the "systemic" vessels were compressed from without over a considerable length. This maneuver increased "systemic" resistance as before and also, by forcing fluid into other parts of the system, raised the static pressure. Therefore, by suitable adjustment, "systemic arterial" pressure and flow could be restored to normal. In this case "venous" pressure remained elevated, and the pressure relations simulated clinical heart failure.

In a third attempt, additional fluid was added to the circulation. This also restored "cardiac output" and work, and "arterial" pressure to normal; and, as the static pressure was increased, the "venous" pressure remained elevated (Table 1, 1D). The effect of this maneuver was to simulate not only the pressure relations of clinical congestive failure, and the normal cardiac output demanded by Harrison's views,[7] but also the increased blood volume[5] and the increased static pressure found in this condition.

In our schema, to simulate the pressures found in clinical congestive heart failure, extracardiac forces which raise the static blood pressure are needed.

Analysis of Certain Hydraulic Factors Concerned With One-sided "Heart Failure." Experiments 2 and 3, Table 1, show the effects which follow one-sided heart failure in the schema.

Although the transference of fluid from the "pulmonary" to the "systemic" side, or vice versa, may be very conspicuous after mechanically obstructing the flow, this effect is small after weakening the right side of the "heart." There are two reasons for this: First, weakness of one "heart" always weakens the other also, so that the disproportion in strength is not as great as one would expect. Second, the volume of the "systemic" system is much larger than that of the "pulmonary" system. For this reason transference of a small percentage of the fluid in the "systemic" side to the "pulmonary" side affects the presssures in the smaller circuit profoundly, but a large percentage of the contents of the "pulmonary" circuit must be moved into the "systemic" side before much change in the "systemic" pressures occurs.

The Relation of the Schema's Behavior to Certain Clinical Conceptions of Cardiac Failure. Many authors[4,7] believe that, when a patient exhibits congestion of systemic veins, right-sided heart failure should be diagnosed. Similarly when the lungs are congested, the left heart is believed to be inadequate. That these two conceptions were not physiologically identical has not been realized.

The normal human lungs, with their capillary blood and a variable amount of their arterial and venous blood, weigh only about 1000 gm. at autopsy.[17] The heart and lungs of recently killed rabbits contain an average of 22.8% of the total blood volume.[12] By dye injections in man, Hamilton, Moore, Kinsman, and Spurling[6] estimate the volume of blood between the antecubital veins and the brachial artery to be about 2 liters normally; an estimate which includes the blood in the heart, in the systemic great veins, and in the systemic arteries to the point of puncture, in addition to the blood circulating in the lungs. When 500 cc. or more of blood is transfused into the systemic veins of patients without heart disease, the extra blood is doubtless distributed throughout the vascular system. The large proportion remaining on the systemic side causes no increase of venous pressure at all comparable with that found in congestive failure. Therefore we find it hard to believe that much of the increase of systemic venous pressure in congestive heart failure can be attributed to the transference to the systemic system of blood which could be spared from the lungs. On the other hand, it seems entirely reasonable to expect that transference of blood from the larger systemic to the smaller pulmonary side might be an important factor in the causation of the pulmonary congestion which has long been believed to follow failure of the left heart in clinical conditions.

Therefore we believe that weakness of the right heart, uncomplicated by any other physiologic changes, would not be followed by congestion of the systemic veins to the extent seen in congestive heart failure. However, if additional factors were present which had

previously increased static blood pressure, as an increase in blood volume or a general vasoconstriction might do, weakness of the right heart would have a much greater effect on venous pressure. For, in the first case, the blood transferred from the lungs would be accommodated in the flaccid systemic vessels with little increase of pressure; in the last, added to vessels already tense, it would increase the venous pressure much more.

The relation between right heart failure and systemic venous congestion is not as simple and direct as has been generally assumed when the one is so confidently diagnosed from the presence of the other.

Conclusions. A circulation schema is described whose pumps obey Starling's Law of the Heart.

On this schema the static blood pressure, *i. e.*, the pressure existing at all points in the circulation when the "heart" is stopped, is an important factor in compensation for weakness of the "heart" and in the causation of increased "venous" pressure.

The arterial and venous pressures of clinical congestive failure cannot be reproduced in this schema by weakening the heart alone. Mechanisms which cause an increase of static blood pressure, such as general vasoconstriction, pressure on vessels from without, or the insertion of additional fluid within the vessels, must be introduced before the pressure relations of clinical congestive heart failure can be reproduced.

The behavior of our schema has suggested clinical considerations which raised doubt in our minds whether the venous congestion of "congestive heart failure" was brought about in the manner commonly believed. This prompted the clinical investigation reported in the following paper.

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RÔLE OF THE "STATIC BLOOD PRESSURE" IN ABNORMAL INCREMENTS OF VENOUS PRESSURE, ESPECIALLY IN HEART FAILURE.

II. - Clinical and Experimental Studies.

By Isaac Starr, M.D.,
Hartzell Professor of Research Therapeutics, University of Pennsylvania, Philadelphia, Pa.

In the preceding paper a schema of the circulation was described[17] which, we believe, mimicked physiologic conditions more closely than its predecessors. Studying the behavior of this schema we were impressed with the importance of the static blood pressure, *i. e.*, the pressure present throughout the circulation when the heart had stopped. For instance, after the heart had been weakened, mechanisms which raised static pressure had to be introduced before the arterial and venous pressures found in clinical congestive heart failure could be simulated. Also, increasing static blood pressure proved to be a method of partial compensation for weakness of the heart, for a measured weakening of one or both of the schema's "hearts" caused far less diminution of circulation when the static pressure was high than the same degree of weakening when this pressure was low.

Obviously, therefore, it seemed important to obtain data concerning the static blood pressure in clinical conditions. This was undertaken by making preparations in advance, waiting till the heart stopped at death, and then measuring this pressure by the introduction of a needle into a vein or, more conveniently, into the right ventricle. This measurement has been made in 64 patients with subsequent necropsies in about 70%.

The results show that cases dying with prolonged and severe congestive failure have a static blood pressure much higher than that found in persons dying of other causes. The differences found are sufficient to account for a large part, in some instances for all, of the differences in venous pressure found during life.

Therefore it appears that a large part of the force causing the increment of venous pressure in congestive failure is not derived directly from the heart for it persists when the heart is no longer functioning.

The author recalls an observation made when he was an intern, called to pronounce the death of a cardiac patient. With the body still supported on a back rest at 45°, the veins of the neck were distended as they had been during the last illness. I have repeated this observation many times since and do not doubt that many readers will recall the same fact. Therefore this investigation is but a quantitative study of a finding which may be familiar to many.

But I have found neither record of the fact nor discussion of its significance.

Technique. For measuring static blood pressure an 18-gauge needle, 3½ inches long, attached to a Luer-Kaufmann side-arm syringe was employed. The side arm was connected, through a T tube and pinchcocks, to a manometer of 3 mm. bore, and to a reservoir. The system was filled with either 0.9% NaCl or 0.5% sodium citrate. The heart, or occasionally a vein, was punctured and blood was drawn into the syringe until the side arm was opened. Then fluid was allowed to flow from the manometer as far as it would, care being taken that the syringe plunger was not drawn in as the pressure fell. This maneuver was repeated several times until the needle was washed free of blood and constant readings were obtained. The manometer was then lowered and the rise of the column to its previous level observed. Due to the viscosity of blood which now entered the long needle the level of the initial readings was often not attained with exactitude. The readings obtained with a falling column were considered correct, the attainment of approximately the same level by the rising column being regarded as a check on the patency of the system. A correction, made necessary by capillarity and by the force required to make fluid flow through needle and tubing, was applied to each reading. It amounted to almost exactly 1 cm. in my apparatus.

The apparatus was placed ready at hand, and I was notified as soon as death was pronounced. The great majority of the measurements were made within 30 minutes of that event. If death occurred at night the interns, after instruction in the technique, made the readings. The subject was always placed flat on his back when the estimations were made.

The plan of the investigation required repeated estimations of venous pressure on many patients. A large amount of the effort was lost, as measurement of static pressure did not always follow. Speed and convenience dictated the choice of method. The capsule methods soon proved too laborious for repeated estimations on different days. I finally came to depend on raising the hand and observing the level at which the veins filled and emptied, the method of Gaertner.[9] A small electric light (Bausch & Lomb whitelite transilluminator), attached to a flashlight battery, was laid on the skin beside the vein and the appearance or disappearance of the well marked shadow made the point of filling or emptying easy to identify. In addition, a direct measurement after venipuncture was made at least once on almost every patient, either using the apparatus described above, a technique adapted from that of Moritz and Tabora,[14] or simply connecting the needle to a small mercury manometer. This experience with several methods left me with a high regard for the rough accuracy of the Gaertner method, if carefully performed. But when patients were extremely dyspneic my results with the Gaertner technique were often somewhat too high and I soon learned to avoid this method under these circumstances. Fishberg[8] cites a similar experience.

There has been no agreement as to the proper base line for venous pressure measurements in recumbent patients. Clark, Hooker, and Weed[5] located the venous pressure reference point of dogs in the great veins. Also it seems evident that the static pressure of patients postmortem should be referred to the center of the body. Therefore to obtain a base line in supine subjects we measured the thickness of the thorax at the level of the junction of the sternum and the 4th rib and used the midpoint. Measurements made at necropsy in a number of cases indicated that this midpoint coincided with the level of the great veins.

Our principal interest in venous pressure concerned its relation to static pressure, so both measurements were referred to the same base line. There-

fore our figures for venous pressure are from 2 to 5 cm. higher than many results in the literature which have been measured from a level either one-third the distance from the anterior to the posterior chest wall, or 5 cm. below the anterior chest wall,[7] the position of the auricles.

Some patients died before venous pressure had been accurately measured. In these cases an impression of the amount the congestion has been recorded in general terms.

Experiments Concerning Certain Properties of the Static Blood Pressure. *Animal Experiments.* Although performed after the clinical investigation had been largely completed the results of the animal experiments can be presented best at this point, as they illuminate the clinical findings.

The ability of mammals to withstand hemorrhage and to receive intravascular infusions without much alteration in blood pressure is conspicuous and it has received much emphasis. Therefore it seemed proper to ask the question whether one had the right to expect that increased intravascular volume would raise venous and static blood pressures.

As no acute animal experiment can be designed to simulate clinical death, I attempted to safeguard the interpretation of the results by diversity in the experiments.

Dogs were employed. Tracheal, carotid, and femoral venous cannulæ were inserted using great care to avoid blood loss. Venous pressures were estimated by allowing very small amounts of saline solution to run into a femoral vein from a manometer. The center of the dog's body was taken as base line.

In Dogs 1, 2, 3, and 4 the experiment was performed while the condition of the circulation was good. The dogs were injected with 2 mg. morphine per kilogram and then given intraperitoneally 1.5 cc. per kilo of a solution containing 2.8% of chloralosane and 42% of urethane. After anesthesia and insertion of the cannulæ, Dogs 1 and 2 received an intravenous infusion of Lilly's acacia diluted to make 6% acacia and 0.9% NaCl. Within 5 minutes after the infusion the dogs were killed by stabbing their hearts with a needle electrode and passing 110 volts D.C. through it. Dogs 3 and 4, having received nothing intravenously, were killed similarly after arterial and venous pressures had been recorded for a few minutes.

In Dogs 5, 6, and 7 similar experiments were performed after the blood pressure had been kept abnormally low for about 1½ hours by deep chloroform anesthesia. Dog 5 developed marked Cheyne-Stokes respiration with varying arterial and venous pressures. Dogs 6 and 7 were given acacia intravenously, Dog 5 serving as control. Dogs 5 and 6 were killed by excess anesthetic, Dog 7 was electrocuted.

The results are charted in Figure 1. In all but Dog 5 a period of struggle followed cessation of cardiac action and the gasping respi-

rations were accompanied by a great elevation of venous pressure which fluctuated with the muscular contractions. Quiet supervened in about 5 minutes and static blood pressure, similar in artery and vein, is recorded from that point. The curve obtained is very similar in all the animals. It descends from the high level reached in the struggle, and levels off about 20 minutes postmortem. After this the change does not exceed 1 cm. and the variation may be either up or down. Dogs 4, 5, and 7, followed for an hour postmortem showed no further change from that recorded. At the end of that time the blood had not clotted and the muscles contracted vigorously on electrical stimulation.

The form of the postmortem pressure curve in these dogs is similar to that found in rabbits by Riml.[15] The height of the curves of the control animals agrees well with the value found in rabbits by that author and with the average found in the control group of patients to be described.

The amount of acacia solution added, in per cent of the dog's probable blood volume, estimated as 7% of the body weight, is shown in Figure 1. It will be seen at once that, despite the diversity of the experiments, the results arrange themselves almost exactly in the order of the intravascular volumes. The interchange of position of the results secured in Dogs 1 and 7 may be due to differences in the condition of their circulations, or to differences in the anesthetic employed. It is, therefore, entirely proper to think of increased intravascular volume as a cause of increased static blood pressure.

The results obtained before the animals were killed indicate that increased intravascular volume can raise venous pressure also, as has long been known.[16c]

Clinical Experiments. These were performed postmortem before the blood clotted.

Case 33, apparently improving, collapsed while I was making ward rounds. Respiratory efforts persisted for about 5 minutes. Measurement of static blood pressure began 12 minutes postmortem. The results are charted in Figure 1 as curve A. The form of the curve is similar to that obtained in the animal experiments. Confirmation of the rapid fall occurring soon after death was obtained in another patient who died of pulmonary infarction during ward rounds. The static blood pressure was determined 10 minutes after death and fell about 1.5 cm. in the next 2 minutes when observations had to be discontinued.

No similar rapid change in pressure was found in any other case in the series. Evidently measurements began after the curve had leveled off. In 15 patients estimations repeated for an hour showed very little change with time. In one there was a fall at the rate of 1 cm. per 15 minutes. Changes in the other cases were smaller.

Slow drifts both downward and upward were seen, as in the animal experiments.

When the blood had clotted or rigor mortis had set in, the pressure within the circulation sometimes differed greatly from that obtained earlier. The change was in either direction. Values obtained so long postmortem; though often identical with those obtained earlier, are not to be trusted.

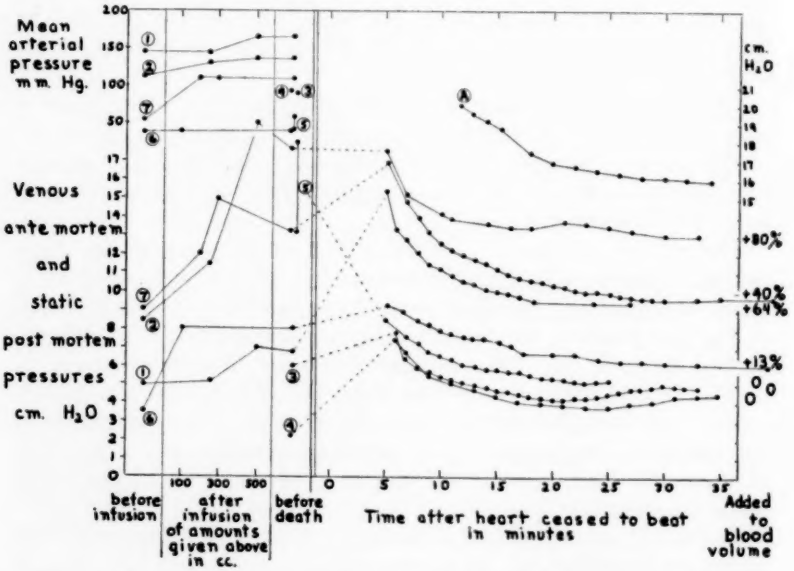

FIG. 1.—Results of animal experiments. The numbers correspond to the dogs mentioned in the text. Values charted to the left of the double line were obtained during life and represent arterial and venous pressures. Dogs 1, 2, 6 and 7 had intravenous infusions and the values obtained before, during, and after the infusions are recorded. To the right of the double line measurements of general static blood pressure are recorded at the time postmortem at which they were made. The first of these values is connected by a dotted line with the last value of the venous pressure obtained antemortem in the same dog. In the right hand margin is shown the amount of the infusion in per cent of the dog's probable blood volume calculated from his weight, for each animal. The curve *A* shows the change of general static blood pressure with time in Case 33.

Occasionally small rhythmic fluctuations in the static blood pressure made one wonder if all vital activity had ceased. Similar fluctuations were seen in the animal experiments. In a number of instances I attempted to demonstrate a persistence of vascular activity in the patients by injecting histamine and adrenalin into the skin. There was no visible response in any case.

Several experiments were made to throw light on the possibility that when the static pressure was high, it would diminish more rapidly in the period before measurement could be made because

blood was forced from the lifeless vessels at the higher pressures. In four experiments the static pressures were forced up by laying heavy weights on the abdomen, in one the same result was secured by injecting fluid into the peritoneal cavity. Thus in Case 7 this pressure, steady at 19.8 cm. for 19 minutes, was increased to 29.5 cm. by laying 20 lbs. on the abdomen. During the next 10 minutes it fell slowly to 27.6 cm., after removal of the weight it was 18.5.

In another experiment the static pressure changed from 10.57 to 13.8 on weighting the abdomen and remained unchanged at the higher level for 15 minutes. After removal of the weight the pressure was 9 cm. The other results were similar. Generally there was evidence of a slow drift downward at the higher pressures. But part of this effect may have been due to the expulsion of flatus by the abdominal compression, which was painfully obvious in most cases. Our evidence indicates that the rate of change is only slightly faster when the pressure is high. The results of the animal experiments permit a similar conclusion.

When the heart stops the pressures throughout the vascular system would equalize only if the vessels remained open. To safeguard ourselves on this point we twice made simultaneous estimations of pressure in a peripheral vein and in both ventricles, the position of the needles being verified at necropsy. We have also compared pressures in a peripheral vein and in the right ventricle in 11 cases. In all but 2 cases the agreement was within 1 cm. of water, a difference certainly within the error of the methods. In 2 cases differences between vein and heart pressures of 3.5 and 5.5 cm. are doubtless to be attributed to technical errors or to local venous obstruction. However experiments with a circulation schema containing a fluid of the same viscosity of blood[17] have shown that small differences in pressure may persist in different parts of the circulation for a long time after the pumps have been stopped.

Opening the vessels, as by the pathologist's incision, is followed immediately by diminution of static blood pressure. Intravenous injections raise this pressure. Thus in Case 32, with a static pressure of 9.5 cm. 150 cc. 5% acacia intravenously raised this pressure to 12 cm., a total of 295 cc. to 13.2 cm., 485 cc. to 14.4 cm., 635 cc. to 15 cm. These findings indicate that small changes in volume, such as might be due to the difference between the heart stopping in systole or diastole, or to the injection of small amounts of fluid in measuring the pressures, would have but little influence on our results. They also indicate that the larger increases in intravascular volume found in congestive failure[10] are sufficient to increase the static pressure to the value we find.

Pressure on the abdomen was followed by a prompt rise of static blood pressure. If the abdomen was flaccid this rise was small, if tense it was large. Thus in 1 case a weight of 40 lbs. laid on the flaccid abdomen increased the pressure 3.6 cm. In 2 cases whose

TABLE 1.—CLINICAL DATA.

(Numbers in parentheses indicate the number of the day before death on which the observation was made.)

Case.	Age.	Sex.	B.P. (mm. Hg).	Venous congestion		Static pressure (cm. H_2O).	Remarks. Clinical diagnosis and pertinent necropsy findings.
				Duration (days).	Amount or pressure (cm. H_2O).		
					Group 1. Congestive Failure the Important Cause of Death.		
M. H. 1	47	F	140/70	250	Moderate	21	Rheum. ht. dis. aur. fib. Necropsy: chronic rheum. mitral and aortic valvulitis. Passive congestion of liver and lungs.
M. S. 2	18	F	130/80	60	Marked	25	Subacute Bact. Endocarditis. *Strep. viridans.* Nec.: congenital septal defect, S.B.E. of all valves. Pass. cong. lungs, spleen, liver, etc.
J. McQ. 3	26	M	130/70	3	Marked	17.5	R.H.D. 4th attack of congestive failure. Mitral and aortic valvulitis. No nec.
J. O. 4	58	M	150/80	180	16 (1)	18	Nec.: chron. rheum. mitral and tricuspid valvulitis, pass. congest. lungs and abd. organs.
N. B. 5	37	M	238/158 (4) 105/70 (1)	14	36 (4) 38 (1)	23.5	B.U.N. 113. Uremia. Cardiac hypertrophy and congestive failure. Nec.: (kidneys only) malig. nephrosclerosis.
E. L. 6	56	F	125/95	30	26 (1) 32 (0)	18.2	Diabetes since 1931. Nec.: Ht. 800 gm. Rheum. ht. dis. Coronary sclerosis, left-sided hypertrophy, right-sided dilatation. Phlebotomy 350 cc. before death.
G. C. 7	28	M	150/50	30	Moderate	21	Luetic ht. dis. Aortic regurg. Rt. pleural effusion, tapped. Congest. ht. failure. No nec.
M. L. 8	32	F	178/128	5	11 (19) 9 (6) 23 (2) 24 (1)	20	Nec.: Advanced arteriolonephrosclerosis. Heart 330 gm. left vent. hypertrophy. 200 cc. fluid in pericardium. Massive hepatic necrosis.
P. R. 9	40	F	190/110	21	19.5 (12) 30 (12) 19 (9) 19 (3) 16 (1)	20	Terminal cardiac failure and uremia. Nec.: chronic glomerulonephritis. Heart 350 gm. Pericardium coated with exudate, contains 200 cc. fluid. 2d estimate of V.P. made when patient's abdomen was greatly distended. There was no distention when the other estimates of V.P. were made.
W. E. 10	30	M	120/80	30	20 (3)	23	Nec.: chronic rheum. mitral and pan-valvulitis, active; myocardial dilatation. Passive congestion lungs and abd. viscera.
					Group 2. Congestive Failure Present at Some Time But Not the Chief Cause of Death.		
A. J. 11	38	M	250/140	Unknown	None recorded	19.5	Nec.: malignant nephrosclerosis. Extreme edema of brain, edema and congestion of lungs, liver moderately congested. Heart 590 gm. L.V. hypertrophy. I did not see patient during life. This case perhaps belongs in Group 1.
C. J. 12	58	M	130/90	Temporary 3	25 (8) 11 (6) 16 (2) 11 (1)	13.8	Urethral stricture and infected fistulæ. Edema and venous congestion cleared up after treatment. Died after suprapubic cystostomy. Nec.: acute cystitis, nephrosclerosis. Ht. 800 gm., multiple infarcts, coronary sclerosis with occlusion, fibrinous pericarditis, hypertrophy, dilatation.
N. S. 13	52	M	185/120	1	Slight	13.5	Former hemiplegia. Hypertensive ht. dis. Pulmonary infarction. No nec.
S. D. 14	70	M	100/30 (1)	..	13 (1)	13	Asthma. Art. ht. dis. Coronary occlusion (?). No nec.
A. Z. 15	63	F	130/72	Transient 7	18 (12) 21 (8) 14 (4) 14 (3)	15	Auricular fibrillation. Nec.: recent post. coronary occlusion, multiple infarcts of lungs. Received saline intravenously in large amounts up to 2d day before death.

					14 (4)		
					14 (3)	15	
T. O'N. 16	50	M	214/140	Transient 21	23 (50) 22 (31) 11 (17)		Congestion cleared up under treatment, finally died of uremia and terminal erysipelas. Nec.: malignant arteriolonephrosclerosis. Ht. 755 gm. L.V. hypertrophied, fibrinous pericarditis.
					11 (6)	15	
D. DiF. 17	56	M	120/70	Terminal event 1	Slight	15.3	Angina pectoris. Cardiac silhouette + 100%. Auricular fibrillation. Old infarct? No nec.
A. W. 18	56	F	190/60	Transient 2	23 (2)	16	Chronic arteriolonephrosclerosis, cardiac hypertrophy, auric. fib., uremia. Received 1000 cc. saline daily by vein. No nec.
A. K. 19	45	F	250/155	Terminal event 2	13 (17) 41 (2)	16	Chronic glomerulonephritis with uremia. Cardiac hypertrophy, orthodiagram + 53%. No nec.
D. S. 20	68	F	170/90 (5)	Transient 10	19 (13) 19 (4)		Admitted in congestive failure which cleared up under treatment. Died from encephalitis from an infected sinus. Hypertensive ht. dis. Cardiac hypertrophy. Aur. fib. No nec.
			130/50 (1)		15 (2)		
					14 (1)	7.5	
O. G. 21	50	M	190/110 (3)	Terminal	12.5 (3)		Nec.: heart 670 gm. Marked hypertrophy, coronary sclerosis. Cerebral arterioscl. with ventricular hemorrhage.
			105/65 (2)	event 2	27.5 (2)	14.5	
					Group 3. Cases of Heart Disease Dying Without Edema or Congestion.		
H. S. 22	39	M	120/70	...	None	16	Nec.: chron. rheum. valvulitis, subacute bacterial endocarditis, metastatic encephalitis with cerebral hemorrhage. Passive congestion of lungs and abdominal viscera.
I. F. 23	20	F	120/72	...	15 (1)	0.5	Old rheum. ht. dis. Sub. bact. endocarditis, cerebral embolism. No nec.
			70/55 (1)				
L. R. 24	53	M	124/80	...	None observed	9	Bronchial asthma. Art. ht. dis., cong. failure in 1934, recovered. Nec.: (1936) Ht. 700 gm., extreme hypertrophy, myocardial infarct with mural thrombosis. Thrombosis basilar artery of brain. Bronchopneumonia.
R. T. 25	70	F	190/100	...	11 (1)	8	Hypertension known 2 yrs. Fell unconscious. Ht. enlarged. Aur. fib. Diagnosis cerebral hemorrhage. No nec.
J. M. 26	58	M	90/70	...	13 (3)	7.5	Sudden precordial pain. Diagnosis acute myocardial infarction, ant. wall left vent. No nec.
K. D. 27	47	M	130/75	...	11 (3)	7.5	In cong. failure 1934, recovered. In 1936 fever and purpura. Nec.: acute necrotic enteritis, ht. 470 gm., rheum. mitral valvulitis, hypertrophy, mod. coronary sclerosis.
H. F. 28	65	F	130/75	...	8 (3)	12	Nec.: multiple myeloma, bronchopneumonia. Ht. 360 gm., old rheum. valvulitis.
M. B. 29	41	F	120/75	...	None	14.5	Nec.: adenocarcinoma of lung. Ht. 260 gm. 250 cc. bloody pericardial fluid, metastatic pericardial adenocarcinoma, active rheum. mitral valvulitis. Passive cong. of liver.
J. B. 30	41	M	100/60	...	7 (0)	13	Old angina pectoris. Severe precordial pain, in shock when V.P. was measured. Nec.: Ht. 430 gm. Multiple coronary occlusions with myocardial infarcts. Marked coronary sclerosis.
L. B. 31	35	F	216/164	...	None	9.5	Nec.: malignant nephrosclerosis. Ht. 350 gm. L.V. hypertrophy, fibrinous pericarditis, marked coronary sclerosis.
J. J 32	63	M	130/80	...	12 (7) 12 (5)		Diabetes mell. Legs amputated, last in 1935. Infection of stump. Nec.: (1936) cellulitis of stump, terminal septicemia. Heart: Septic thrombosis rt. auricle,
					12 (3)	9.5	mod. coronary sclerosis.
S. G. 33	20	M	215/130	...	None recorded	16	Died suddenly. Nec.: chronic glomerulo-nephritis. Pul. edema. Pass. cong. of liver and spleen. Edema of brain. Ht. 505 gm. L.V. hypertrophied.
J. E. 34	36	M	130/70	...	None	10	Congestive failure 1935, recovered. Auric. fib., jaundice, fever, cholecystostomy. Died 2 mos. postop. Nec.: chron. rheum. mitral valvulitis, cholecystitis, hypertrophic cirrhosis, terminal septicemia with ulcerative endocarditis.
					Group 4. No Cardiac Disease.		
L. P. 35	40	M	120/80	60?	R 45 (3) L 58 (3) R 48 (1)		Venous pressure measured both arms. No congestion of leg veins. Nec.: primary bronchogenic carcinoma, mediastinal metastasis obstructing superior vena cava, multiple visceral metastases.
					L 58 (1)	6.5	

Remainder of this group, see Table 2.

abdomens were more tense 20 lbs. increased this pressure 7.3 and 9.8 cm. In 1 distended case 40 lbs. elevated this pressure 17 cm. The rapid response of the manometer to pressure on the abdomen proved a handy way of assuring oneself that manometer fluid and blood were in pressure equilibrium.

Arrangement and Results of the Clinical Study. The 64 cases have been divided into 5 groups. Pertinent data concerning clinical and necropsy findings and the results of measurements of venous and static pressures in these cases have been given in Table 1. Figure 2 summarizes the static pressures.

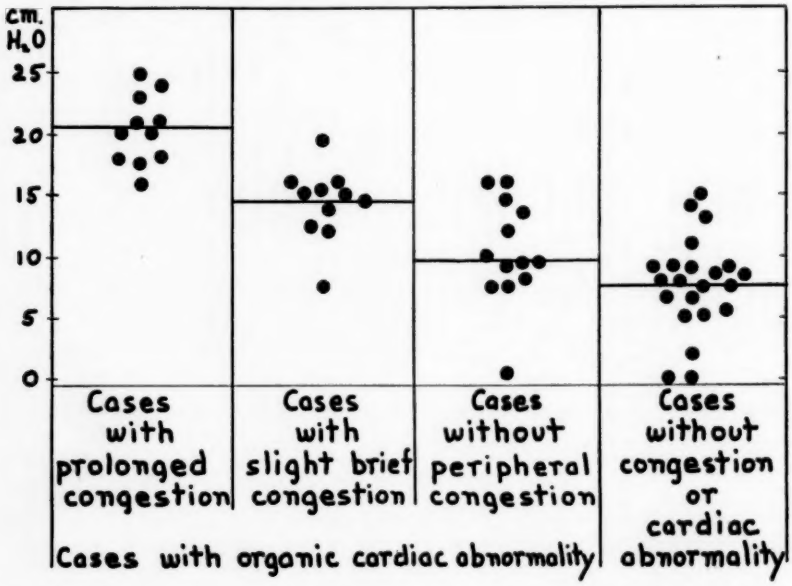

FIG. 2.—The static blood pressures in various groups of cases. The cross bars indicate the average values. The mean of Group 1 is significantly different from the means of Groups 3 and 4 (for $P = 0.05$), and it just fails to attain a similarly significant difference from Group 2. The means of Groups 3 and 4 are not significantly different from each other.

The cases placed in the first three groups all had some organic cardiac abnormality. In Group 1 have been placed 10 cases in which congestive heart failure was judged to be a major, if not the sole, cause of death. In Group 2 have been placed 11 cases in which congestive failure was present at some time during the course of the disease but it either cleared up before death or appeared to be a brief terminal event in patients dying from another cause.

In Group 3 have been placed 13 cases in whom neither venous congestion, nor "cardiac" edema was observed at any time during life. However, in Cases 22 and 29, passive congestion was demon-

strated at necropsy and this was doubtless the factor which made their static pressures the highest of the group. If these 2 cases are promoted to Group 2 the average static pressure of Group 3 is reduced from 9.7 to 8.4 cm.

Group 4, the control group, consists of 25 cases characterized by essentially normal hearts. Their static pressures average 7.2 cm. (Table 2).

TABLE 2.—COMPARISONS OF VENOUS CONGESTION (ANTEMORTEM) AND STATIC PRESSURES (POSTMORTEM) IN PATIENTS WITH NORMAL HEARTS.

Case.	A.M. venous congestion or pressure (cm. H_2O).	P.M. static pressure (cm. H_2O).	Necropsy.	Chief diagnosis and remarks.
Group 4. No Cardiac Disease.				
J. M.	14	14	Yes	Myel. leukemia; recurrent ascites
M. M.	None	2	Yes	Polyposis of colon; anemia
J. H.	None	9	Yes	Ca. pancreas
F. D.	None	15	Yes	Ca. esophagus
J. S.	None	7.5	Yes	Cholelith., peritonitis
W. A.	None	5	Yes	Ca. of tongue
S. P.	None	5	Yes	Meningitis
S. C.	None	8	No	Chronic nephrosis
A. R.	None	8	Yes	Strep. pneumonia
W. A.	9	8.5	Yes	Meningitis
F. W.	10	0	Yes	Pul. tuberculosis, purpura
C. W.	13	9	Yes	Bronchopneumonia
J. W.	10	11	Yes	Lymphosarcoma
A. C.	None	9	Yes	Ca. gall bladder
M. S.	None	6.5	Yes	Ca. breast
C. B.	10	9	Yes	Diabetes mel. septicemia
J. R.	11	0	Yes	T.B. meningitis
A. M.	15	8.5	Yes	Lobar pneumonia (distended when V.P. was taken, not at death)
R. O.	5.5	7.5	No	Meningitis
J. O.	8	13	No	Bronchopneumonia
K. W.	None	5.5	Yes	Lung abscesses
J. D.	15	0	Yes	Empyema
P. P.	8.5	7.5	No	Ca. lung
J. P.	10	7	No	Ca. stomach
L. P.	..	..	..	See Table 1, Case 35
Group 5. Cases Dying With Marked Abdominal Distention.				
M. O.	..	23	Yes	Lobar pneumonia
F. A.	..	19	No	Lobar pneumonia
X. S.	..	13.5	Yes	Myel. leukemia, hemorrhage
I. D.	..	14.5	Yes	Gen. peritonitis

In a special fifth group have been placed 4 cases; their data will be found in Table 2. Each of these died with marked abdominal distention. The static blood pressures were high in this group, averaging 17.2 cm., a result consistent with the observation that when intraäbdominal pressure is increased intentionally the static blood pressure rises.

Figure 2 shows the individual and average static blood pressures in the first four groups. Obviously the static pressure may have been influenced by the treatment employed in several cases. When transfusion or venesection was employed as a last resort this is noted in the tables. Slow intravenous saline infusions were used occasionally and, thinking that the resulting pressure changes would be small and transient, we have included these data.

Discussion. *Certain Fundamental Difficulties and Assumptions.* One must ask whether the static blood pressure obtained postmortem truly represents the corresponding pressure present during life. The results of experiments on animals bear on this question. Starling,[16a] after sectioning the cord to prevent asphyxial vasoconstriction, stopped a dog's heart by stimulating the vagus. Three minutes later the blood in arteries and veins was in pressure equilibrium at 8.3 cm. H_2O. After the curve had leveled our control dogs showed an average postmortem blood pressure of about 5 cm. H_2O (Fig. 1). But section of the cord affects vascular tone and the experiments may not be comparable.

When I stopped the heart by stimulating the vagus,[16a] an experiment I tried repeatedly in Dogs 1 and 2, struggle and asphyxial vasoconstriction supervened before the pressures in arteries and veins equalized. So I was unable to discover a level during life which could be compared with that found postmortem.

The expectation is that, because of vascular and muscular relaxation, the static pressure diminishes postmortem. Therefore the value obtained when it has become stationary is probably somewhat smaller than the corresponding pressure present before death. But the change is probably much smaller than the difference between the initial and final postmortem pressures shown in Figure 1. Asphyxial vasoconstriction and muscular activity were undoubtedly factors in the values first obtained in these experiments.

Conclusions must be drawn on the assumption that the change in static pressure is equal, on the average, in the various groups of patients, so that the differences found after death represent differences present during life. This assumption is supported by the results of the experiments on dogs (Fig. 1). The falling postmortem pressure curves remain discrete and arrange themselves nearly in the order of the intravascular volumes present during life.

However, in the patients whose static blood pressures were forced up postmortem, the elevated curves diminished somewhat faster than the lower ones. The animal experiments showed a similar result. Therefore the differences found postmortem in our cases may somewhat underestimate the differences present during life.

The objection might be raised that some special feature of congestive failure, associated with death by slow failure of the circulation, might prevent the drop of the postmortem pressure curve in these cases and so account for the differences found. One can only point out that lack of oxygen would be expected to increase capillary permeability in congestive failure, and that the cases of coronary thrombosis in Group 3, also dying with gradually failing circulations, showed no comparable elevation of static blood pressure. Cases of heart disease, dying without congestion, do not have high static pressures.

It seemed possible that the height of the blood proteins might

influence the results by controlling the rate of diffusion of fluid from the blood. Blood proteins had been estimated before death in 12 patients, the results ranging from 3.6 to 6.7%. When these figures were plotted against the corresponding static pressures the points were so widely scattered that it seemed evident that the amount of blood proteins was no important factor in our results.

Interpretation of the Results. The behavior of the circulation schema permits one to classify the factors which may increase venous pressure as:

Group 1. Factors causing transference of blood from arteries to the veins. Cardiac weakness, slowing of the circulation from any cause, or diminution of peripheral resistance, would bring about effects of this kind.

Group 2. Factors causing transference of blood from the systemic to the pulmonary system, or *vice versa*. Weakening only one side of the heart relative to the resistance it must overcome, while the strength of the other remained intact, would cause effects of this kind.

Group 3. Factors causing increased static pressure; due to (*a*) increased intravascular volume sufficient to stretch the vessel walls, (*b*) vasoconstriction, or (*c*) pressure on blood-containing vessels from without. Unlike the factors in Groups 1 and 2, the agents which bring about such changes of static pressure are not immediately connected with the heart. If there is any connection it must be a remote one with steps in between.

Factors of Groups 1 and 2 cause readjustments inside the circulation. They are directly due to the heart and when the heart stops all evidence of their previous presence disappears. They do not affect static pressure. The factors in the last group are not directly due to the heart and they cause an increment of pressure which persists after the heart has ceased to beat.

Since cases of congestive failure have a higher static pressure after death than controls it seems obvious that factors of the third group must have entered into the increment of venous pressure present during life. The next question is, what percentage of this venous pressure increment can be properly attributed to these factors?

The static pressure in cases dying in congestive failure averages 20.7 cm. of H_2O, in cases dying without heart disease it averages only 7.6 cm., the difference is 13.1 cm. of water. According to Eyster[7] the venous pressure of normal persons is from 4 to 6 cm. H_2O, this pressure in the 6 cases of cardiac decompensation given in his Table 1 averages 19 cm., 14 cm. above the normal average. Villaret *et al.*,[18] measuring from a different base line, call the normal venous pressure 13 and 12 cm. H_2O for men and women, respectively. In the 7 cases of congestive failure reported the average venous pressure was 28 cm., 15.5 cm. above the normal average. Our

results are very similar. Apparently the average difference between the static pressures is sufficient to explain over 85% of the average increment of venous pressure found in congestive failure.

But in certain individual cases the results point to a different conclusion. In Cases 5, 19, and 21, all with hypertension, the elevation of static pressure will explain less than half of the venous pressure increase found during life. In Case 35, with mediastinal obstruction of the veins, the static pressure played no part at all in a maximum rise of venous pressure. Obviously other factors were operating in these cases. On the other hand, in the case of mitral stenosis, Case 10, in which right-sided failure might have been diagnosed, and the presence of the cardiac factors of Groups 1 and 2 expected, the static pressure accounted for all the increment of venous pressure.

Returning to the discussion of the average results one may ask what causes the average increment of static pressure in congestive failure. One factor is surely the increased blood volume found in this condition, a view put forward by Bolton[2] from results of animal experiments to be described. A relationship between venous pressure and blood volume in clinical congestive failure has been demonstrated by Brandt[3] and, using better methods, by Gibson and Evans[10] who review the other literature consistent with this conception.

Certainly other factors may contribute to the increment of static pressure in certain cases. Pressure exerted on vessels from without, as by edema or fluid in the body cavities, would also cause increased static blood pressure persisting after death, if there were no compensatory decrease of blood volume. The results obtained in the 4 cases of Group 5 who died with extreme abdominal distention give evidence that such factors exist. Their static pressures averaged 9.6 cm. above the average normal level although their hearts were normal. Also I have observed the venous pressure to increase markedly when distention was present (Case 9) and to diminish as soon as it was relieved. Clark[4] found venous pressure to diminish after tapping the chest in 7 of 8 cases and he described the relation of venous pressure and urine volume as inverse and coincident in 6 cases of congestive failure. We have similar data in 5 cases. These results are consistent with the view that fluid or gas in the body, sufficient in amount to compress the adjacent vessels, is a factor in the elevation of the static, and so of the venous, pressure.

General vasoconstriction or increased muscular tone[12] would certainly be a factor in the static pressure. It is impossible to say definitely how much vital factors of this kind contribute to the static pressure as we measure it postmortem. One is tempted to think that muscular relaxation causes the fall which occurs during the 15 or 20 minutes after the circulation has stopped, and that the leveling after that time indicates that vital activity has largely ceased. But strips of human arteries, obtained at amputation by

Cow,[6] when placed in oxygenated Ringer's solution at 37°, maintained their power of reaction to stimulæ for several hours without impairment. On the other hand, neither adrenalin nor histamine, injected into congested areas of skin when non-cardiac pressure was measured, caused any visible response in several of my patients.

The sum of the results given above drives one to attribute the largest part of the venous pressure increment in most cases of congestive failure to factors such as increased blood volume and pressure on the blood in the vessels by fluid or gas within the body. Our data shows that other factors are more important than these in only a few cases.

The Relation of Our Results to Conceptions Derived From Animal Experiments. Starling[16a] attempted to simulate cardiac failure in animals by injecting oil into the pericardium. The results led him to develop the mechanical theory of edema formation which bears his name. As a logical deduction from this theory he wrote, in 1896, "A condition of hydræmic plethora must be an inevitable physiological consequence of the failure of the heart pump." Starling believed that both plethora and vasoconstriction elevated the static blood pressure in heart failure and that they were factors in the increased venous pressure characteristic of this condition.

Bolton[2] attempted to reproduce the effects of heart disease in cats. In early experiments he diminished the circulation by constricting the pericardium, later he narrowed the superior and inferior venæ cavæ at their entrance to the heart, and finally, he found that the same effects could be produced by narrowing the inferior vena cava alone. Ascites soon followed this operation. Edema appeared early and persisted in the area drained by the obstructed vein. Venous pressure in this same area rose a little immediately after the operation and this was attributed to slowing of the blood stream and to piling up of blood behind the obstruction. A few hours later it fell to normal but then rose as the arterial pressure recovered. This second rise of venous pressure was attributed to vasoconstriction. About a week after the operation the cats began to increase their blood volumes, as estimated by the "wash out" method. The venous pressure in the area of obstruction rose coincidently to a high level. This increase was attributed to the plethora. Excess of fluid intake over urine output was observed. The blood was at first diluted but later regained its usual concentration although plethora continued. Ten to 17 weeks after operation increments up to 40% of blood volume were found.

These experiments have received little attention by clinicians, possibly because of a natural hesitation in granting that partial obstruction of the inferior vena cava was truly analogous to failure of the heart muscle. But from the results of these animal experiments Starling[16b] and Bolton[2] developed a viewpoint of congestive failure the main features of which my results uphold.

Our data indicate that the systemic venous congestion of congestive heart failure is not fully explained as the direct mechanical consequence of weakness of either the right heart or the whole heart. Our evidence indicates that, while increments of venous pressure directly due to cardiac weakness exist, they are minor factors in the clinical pictures of most cases. Therefore the largest part of the venous pressure increment of congestive failure is not directly due to the heart. But these observations give no basis for denying that there might be an indirect relationship with physiologic steps in between. They are consistent, with the finding of normal cardiac output in some cases of congestive failure,[1, 11] and with the view, recently supported by McMichael's data,[13] that venous congestion represents an effort on the part of the body to compensate for weakness of the myocardium by increasing the heart's filling pressure.

But we must not forget that the evidence relating venous congestion to cardiac dysfunction has been weakened by these data. One can now readily conceive of types of venous congestion which might originate from disease of other organs than the heart.

Conclusions. The pressure remaining throughout the circulation after the cessation of cardiac action, the "static blood pressure," has been measured promptly after death in 64 patients. Necropsies were performed in 44 of these cases.

In persons dying of prolonged congestive heart failure the static blood pressure averaged 20.3 cm. H_2O. In persons dying without heart disease it averaged 7.6 cm. This difference is large enough to account for the major part, in some instances for all, of the high venous pressure found in cases of congestive failure during life.

Obviously, therefore, the larger part of the increase of venous pressure found in congestive failure should not be attributed directly to any difference of cardiac function, for the abnormality persists when the heart is no longer functioning.

Well known theoretical conceptions in congestive failure have been restudied and reassessed in the light of this new information.

I am indebted to numerous members of the Department of Pathology, especially to Dr. O. Norris Smith, for permission to use their necropsy findings and for the performance of certain special studies at my request. The high percentage of necropsies in my cases was due to the skill and energy of the medical residents, Drs. H. F. Flippin and A. W. Terrell, who also assisted the investigation in numerous other ways. My records contain the names of the following interns who made estimations of non-cardiac pressure at night and assisted me in various ways: Drs. W. Jaquette, D. N. Stewart, F. M. Thigpen, W. P. Stewart, T. Lovitt, J. L. Morrison, D. MacL. Wilson, D. Z. Rhoads, J. P. Atkins, L. R. Twyeffort, T. E. Machella, J. G. Smith, H. G. Scheie, A. J. Gaydosh, and R. E. Hobler.

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THE TREATMENT OF PNEUMOCOCCUS PNEUMONIA: A COMPARISON OF THE RESULTS OBTAINED WITH SPECIFIC SERUM AND WITH SULFAPYRIDINE.

By Harry F. Dowling, M.D.,

PNEUMONIA CONSULTANT, HEALTH DEPARTMENT, DISTRICT OF COLUMBIA; CLINICAL PROFESSOR OF MEDICINE, GEORGE WASHINGTON UNIVERSITY,

AND

Theodore J. Abernethy, M.D.,

PNEUMONIA CONSULTANT, HEALTH DEPARTMENT, DISTRICT OF COLUMBIA; ASSOCIATE IN MEDICINE, GEORGE WASHINGTON UNIVERSITY,
WASHINGTON, D. C.

(From the Health Department, District of Columbia, and the Department of Medicine, George Washington University School of Medicine.)

In the short time since Evans and Gaisford[2] made the first report of the treatment of 100 cases of peumococcus pneumonia with sulfapyridine, many investigators have attested to the favorable influence of the drug in decreasing the mortality rate and shortening the clinical course of the disease. The various publications to date have been chiefly concerned with the shortening of the febrile period and the reduction in the mortality rate of the disease, and with the toxic effects of the drug. In general, investigators have obtained mortality rates as favorable as those heretofore reported following the use of specific serum. Actual comparison of the value of sulfapyridine and serum in the treatment of pneumonia has received but slight attention. Therefore, we have attempted to obtain answers to two questions:

1. When comparable groups of cases are treated over the same period of time, will sulfapyridine or will serum be more effective in altering the course of the disease and its mortality rate? and

2. Are there any special situations in which one agent is superior to the other?

From September 1, 1938, through July 15, 1939, 226 cases of pneumonia were treated by us. Of these patients, 90 were given serum alone, 130 sulfapyridine alone, and 6 received both drug and serum. Most of the patients were treated in conjunction with the

Pneumonia Control Program of the Health Department of the District of Columbia in the wards of Gallinger Municipal Hospital and other hospitals of Washington or in homes, while a few were private patients seen in consultation by either of us. The series includes all the adult patients with pneumococcus pneumonia treated by us during this period, no cases having been excluded.

Typing of each patient's sputum was performed at least once and often several times. One or more blood cultures and Roentgen rays were taken on nearly every patient. In addition, cultures were made of all exudates and from the lungs at postmortem.

From August 1 until November 17, 1938, before sulfapyridine became available, patients were treated with serum* alone. After that date, the Type I cases were alternated, one being given serum and the next the drug. When a serum for a particular type was on hand it was used; otherwise the patient was treated with sulfapyridine. There was no selection of cases on the basis of severity, except that both serum and sulfapyridine were given to 6 extremely ill patients.

Results of Treatment. In Table 1 are shown the results of treatment with each of these two therapeutic agents. Pneumonias caused by each type of pneumococcus are listed separately, and, in addition to the total for all types, a sub-total has been calculated for Types I, II, V, VII and VIII pneumonias. The reasons for these types of pneumonias being considered especially suitable for the present comparison are enumerated in the Discussion. Purely for the sake of brevity these pneumonias will be spoken of as the "lower-type" pneumonias.

Mortality Rates. *Types I, II, V, VII and VIII.* Among the 70 "lower-type" pneumonias treated with serum, there were 10 deaths (14.3%). There were 5 deaths among the 52 patients treated with sulfapyridine (9.6%). The 4 individuals treated with a combination of serum and sulfapyridine were severely ill patients; all of them died.

When only the bacteremic cases are considered, it will be seen that there were 3 deaths among 17 patients treated with serum and the same number among 16 patients treated with the drug. The mortality rates are therefore similar: 17.7% for serum-treated and 18.8% for sulfapyridine-treated cases.

Clinicians have long observed that the most effective results are obtained when serum treatment is begun during the first 4 days of the illness. This was true in the present series (as in Table 1) where the mortality rate for patients receiving their first dose of serum during this early period was 10.8%. Early treatment was even more effective in the sulfapyridine-treated cases. The mor-

* Serums for some of the "higher" types were available for testing through the courtesy of the Lederle Laboratories, Inc., and the Gilliland Laboratories, Inc.

tality rate was only 2.9% among the 34 patients receiving sulfapyridine during the first 4 days of the illness.

TABLE 1.—EFFECT OF SPECIFIC SERUM OR SULFAPYRIDINE ON MORTALITY IN PNEUMOCOCCUS PNEUMONIAS.

Type of pneumococcus.	Serum.									Sulfapyridine.								
	All cases.			Bacteremic cases.			Cases treated in first 4 days.			All cases.			Bacteremic cases.			Cases treated in first 4 days.		
	No. of cases.	No. died.	% died.	No. of cases.	No. died.	% died.	No. of cases.	No. died.	% died.	No. of cases.	No. died.	% died.	No. of cases.	No. died.	% died.	No. of cases.	No. died.	% died.
I	31	3		8	1		26	3		23	0		7	0		18	0	
II	*6[1]	2[1]		0	0		5	1		6[1]	2[1]		2	1		3	1	
V	4	0		1	0		3	0		2	0		0	0		1	0	
VII	15[1]	1[1]		4[1]	1[1]		5	0		11[1]	1[1]		4[1]	1[1]		5	0	
VIII	14[3]	4[3]		4[1]	1[1]		7	1		10[2]	2[2]		3[1]	1[1]		7	0	
Subtotal	70[4]	10[4]	14.3	17[2]	3[2]	17.7	46	5	10.8	52[4]	5[4]	9.6	16[2]	3[2]	18.8	34	1	2.9
III	6	1		1	1		3	1		25	1		3	1		15	1	
IV	5[1]	1[1]		0	0		3	1		9[1]	1[1]		2	0		6	0	
VI	2	0		0	0		1	0		2	0		0	0		2	0	
IX	1	1		1	1		1	1		4	0		0	0		3	0	
X	—	—		—	—		—	—		3	0		0	0		0	0	
XI	—	—		—	—		—	—		2	0		0	0		2	0	
XII	3	0		1	0		1	0		3	0		0	0		1	0	
XIII	—	—		—	—		—	—		3	0		0	0		2	0	
XIV	1	0		1	0		1	0		6	1		0	0		2	0	
XV	—	—		—	—		—	—		2	0		0	0		1	0	
XVI	—	—		—	—		—	—		2	1		0	0		1	0	
XVII	1	0		0	0		—	—		1	0		1	0		0	0	
XVIII	—	—		—	—		—	—		6	1		2	0		2	0	
XIX	4	2		0	0		2	0		3	1		0	0		1	0	
XX	—	—		—	—		—	—		1	0		0	0		0	0	
XXI	—	—		—	—		—	—		3	1		0	0		3	1	
XXII	—	—		—	—		—	—		3	3		1	1		0	0	
XXIII	1	1		0	0		1	0		—	—		—	—		—	—	
XXIV	—	—		—	—		—	—		2	0		0	0		1	0	
XXVII	1	0		0	0		1	0		3	0		0	0		2	0	
XXXI	1[1]	0		0	0		0	0		1[1]	0		0	0		0	0	
Total	96[9]	16[9]	16.7	21[4]	5[4]	23.8	60	8	13.3	136[9]	15[5]	11	25[4]	5[4]	20	78	3	3.8

* Cases denoted by superscripts were treated with serum and sulfapyridine combined.

In order to determine the relative severity of the disease in the serum- and sulfapyridine-treated groups, they are compared in Table 2 with respect to age, amount of lung involvement and presence of bacteremia. Among the patients treated with serum, only 18.6% were over 40 years of age, while 36.5% of the sulfapyridine cases were in this age group. More than one lobe was involved in a slightly higher percentage of patients among the serum-treated group (35.7%) than among the sulfapyridine-treated group (30.8%).

One or more positive blood cultures were obtained from 26.6% of the serum-treated patients as compared to 33.3% of the patients treated with sulfapyridine. It will be seen from the above data that the groups of cases treated by the two agents were about equal in severity. More of the sulfapyridine-treated cases were over 40 and were bacteremic; more of the serum-treated cases had extensive involvement.

TABLE 2.—THE EFFECT OF CERTAIN FACTORS UPON MORTALITY RATE IN PNEUMONIAS TREATED WITH SERUM OR SULFAPYRIDINE (TYPES I, II, V, VII, VIII).

		Serum.			Sulfapyridine.		
		No.	Died.	Mortality, %.	No.	Died.	Mortality, %.
Effect of age	12 to 40	57	4	7.0	33	2	6.1
	Over 40	13	6	46.2	19	3	15.8
	% over 40	18.6	—	—	36.5	—	—
Effect of area of lung involved	1 lobe	45	1	2.2	36	2	5.5
	More than 1 lobe	25	8	32.0	16	3	18.8
	% more than 1 lobe	35.7	—	—	30.8	—	—
Effect of bacteremia	Non-bacteremic	47	6	12.8	32	2	6.2
	Bacteremic	17	3	17.7	16	3	18.8
	% bacteremic	26.6	—	—	33.3	—	—

Among the patients of 40 years or less, the mortality rates were practically the same whether serum or sulfapyridine was used (7 and 6.1%, respectively). In keeping with the expected higher death rates in older patients, the mortality rate for patients over 40 treated with sulfapyridine was 15.8%. Among the serum-treated cases, the death rate in this older age group was 46.2%, or nearly three times as great as for sulfapyridine-treated cases.

When the pneumonia involved only one lobe of the lung, the mortality rates for serum- and sulfapyridine-treated cases were again similar, being 2.2 and 5.5%, respectively. When more than one lobe was involved, the mortality rates for both groups were higher, as was to be expected; but, again, the death rate for serum-treated cases (32%) was much more than that for cases treated with sulfapyridine (18.8%).

When bacteremic patients are considered, the mortality rates were practically the same—17.7% when serum was used, and 18.8% when sulfapyridine was administered. The mortality rate in the 47 non-bacteremic patients treated with serum was 12.8%, as against 6.2% for the 32 patients treated with sulfapyridine.

According to these figures, sulfapyridine seemed to be more effective for elderly patients and for patients with two or more lobes involved, while the two agents seemed to be of equal value in bacteremic cases.

Mortality Rates. *All Types.* The totals at the foot of Table 1 give the results of the treatment of pneumonias caused by all types of pneumococci. When all the cases are considered, 16.7% of those treated with serum died, as compared with 11% of those treated with sulfapyridine. Among the bacteremic cases, the percentages were 23.8 and 20, respectively. The same striking reduction of mortality among cases whose treatment with sulfapyridine was begun during the first 4 days of the disease which was noted for the "lower types" of pneumococcus pneumonias was also found in the entire group, only 3.8% of the patients treated within this period dying, as compared to 13.3% of those treated with serum during the first 4 days.

The severity of the two groups of cases may be compared in Table 3. They are quite similar with regard to the proportion of patients with involvement of two or more lobes (32.3% for serum- and 34.6% for sulfapyridine-treated cases); and also with regard to the percentage of bacteremic patients (23.6% and 20.3% for serum- and sulfapyridine-treated cases, respectively). The groups differ in the relative proportion of patients over 40 years, since there are only 23.8% of elderly patients in the serum-treated group, as compared to 31.6% of patients over 40 years among the sulfapyridine-treated cases.

TABLE 3.—THE EFFECT OF CERTAIN FACTORS UPON MORTALITY RATE IN PNEUMONIAS TREATED WITH SERUM OR SULFAPYRIDINE (ALL TYPES).

		Serum.			Sulfapyridine.		
		No.	Died.	Mortality, %.	No.	Died.	Mortality, %.
Effect of age	12 to 40	73	5	6.8	83	5	6.0
	Over 40	23	10	47.8	53	10	18.9
	% over 40	23.8	—	—	31.6	—	—
Effect of area of lung involved	1 lobe	65	6	9.7	89	7	7.8
	More than 1 lobe	31	9	30.0	47	8	17.0
	% more than 1 lobe	32.3	—	—	34.6	—	—
Effect of bacteremia	Non-bacteremic	68	9	13.2	98	8	8.2
	Bacteremic	21	5	23.8	25	5	20.0
	% bacteremic	23.6	—	—	20.3	—	—

Other Effects. In addition to observations on the mortality rates, the effect of a therapeutic agent upon the course of pneumonia may be evaluated from other effects. One of these is the incidence of empyema, developing after treatment has been started. Among the 96 serum-treated cases there were 6 cases of empyema, an incidence of 6.1%, while among the 136 patients treated with sulfapyridine empyema developed in 4 (2.9%).

In Table 4, the two therapeutic agents are compared with regard

to their ability to cause a rapid crisis. The patients who experienced a crisis have been classified according to the number of hours from the first administration of sulfapyridine or serum until the temperature reached 100° F. by mouth, and remained below that figure. In the first column are shown the total number of patients recovering after treatment with either agent. In the second column are the cases terminating within 12 hours after treatment was begun; in the third column those terminating within 18 hours, and in the fourth column, 24 hours. The groups in the three latter columns are not mutually exclusive, since cases terminating within 12 hours are also numbered among those terminating in 18 and 24 hours, and cases terminating in 18 hours are also in the 24-hour group. Percentages of patients who had experienced a crisis by the end of each time period, as compared to the total number of survivors, are given.

TABLE 4.—EFFECT OF SERUM OR SULFAPYRIDINE ON THE RAPIDITY OF THE CRISIS IN PNEUMONIA PATIENTS WHO RECOVERED.

Types of pneumococci.	Treated with:	No. of patients recovering.	Patients with crisis. Within 12 hrs. after treatment begun. No.	%	Within 18 hrs. after treatment begun. No.	%	Within 24 hrs. after treatment begun. No.	%
Types I, II, V, VII, VIII	Serum	60	26	43.3	35	58.3	37	61.7
	Sulfapyridine	47	14	29.8	22	46.8	30	63.8
All types	Serum	80	30	37.5	42	52.5	44	55.0
	Sulfapyridine	121	40	33.1	61	50.4	80	66.1

The most definite results were obtained in the pneumonias caused by Types I, II, V, VII and VIII pneumococci. Among the 60 patients in this group who recovered after serum treatment, a crisis occurred within 12 hours in 43.3%, within 18 hours in 58.3% and within 24 hours in 61.7%. The corresponding figures for sulfapyridine-treated cases were 29.8% for 12 hours, 46.8% for 18 hours and 63.8% for 24 hours. In short, an early crisis occurred more frequently among serum-treated cases, but after 24 hours crisis had occurred as frequently among the sulfapyridine- as among the serum-treated patients.

When pneumonias caused by all types of pneumococci are considered, the same trends are evident, but to a much less degree. In fact, at the end of 24 hours, an even larger proportion of sulfapyridine-treated patients had experienced a crisis (66.1%) than was true of serum-treated patients (55%).

Discussion. We are of the opinion that the fairest comparison of the two therapeutic agents should consider only the cases caused by Types I, II, V, VII and VIII pneumococci. There are several reasons for this: First, these types cause a much larger proportion of typical pneumonias than the remaining types of pneumococci.

Cases caused by Types III, IV, VI pneumococci and the types above VIII are more likely to show a spontaneous recovery within the first few days of the disease. Moreover, a larger proportion of cases in the latter group will run their entire course with only a low-grade fever and little evidence of toxicity. If serum had been available for these mild cases, it probably would not have been used, on the theory that they would recover in any event. On the other hand, if they had been scheduled to receive sulfapyridine, there is more likelihood that it would have been given, since the administration of the drug entails less expense and effort. This factor may have influenced the mortality rate in favor of the sulfapyridine-treated group.

Secondly, serum has been shown to be definitely beneficial in pneumonias caused by Types I, II, V, VII and VIII pneumococci, while the evidence in favor of its value in pneumonias caused by the other types is meager.

Thirdly, Types III, IV and VI pneumococci and those above VIII are frequently found in the throats of normal persons and persons suffering from diseases other than pneumonia. Consequently, although we have eliminated all the cases which were obviously virus pneumonias (as described by Reimann[4]), nevertheless, if a few of these cases are still included, they would most likely be found among the pneumonias of this group. On the same basis as mentioned above, they would be more likely to receive sulfapyridine, if they received any therapeutic agent, and this again may have influenced the mortality rate from the drug favorably.

If we compare the 70 "lower-type" pneumonias treated with serum with the 52 "lower-type" cases treated with sulfapyridine, the drug seems to be slightly more effective than serum in lowering the death rate. This superiority is even more evident among the cases treated during the first 4 days of the disease. Sulfapyridine seems to be superior, also, in the treatment of patients over 40 years and patients with two or more lobes involved, while the two agents appear to be equally effective in bacteremic cases.

When the mortality rates for pneumonias of all types are considered, the results were approximately the same as for the "lower-type" pneumonias, except that there appears to be an even greater superiority of sulfapyridine over serum.

Finland and his associates[3] found a 13% mortality rate for patients treated with serum alone, and a 15% death rate for those treated with sulfapyridine alone. In a third group of patients with more severe pneumonias, treated with a combination of the two agents, 26% died. If we add the group treated with both agents to each group treated by a single agent, as has been done in our study, we find that among 247 of Finland's patients who received serum alone or in combination, 17% died. This figure

corresponds closely to the 16.7% mortality rate for our serum-treated cases. Among Finland's 175 cases treated with the drug, alone or in combination, however, there was a mortality rate of 20%, contrasted with 11% among our cases who received the drug. Perhaps our results with sulfapyridine may have been favorably influenced by the use of sodium sulfapyridine, which was given intravenously to some of the patients.[1]

It should be noted that 20 of Finland's patients who were treated with serum also received sulfanilamide. Since there is some evidence that the combination of sulfanilamide and serum may be more effective than serum alone, this may have had a favorable influence upon the mortality rate in Finland's serum-treated group.

Another phase of our study is confirmed by an analysis of Finland's cases. His figures show that there was a higher death rate among the patients over 40 years treated with serum alone (25%) than in similar patients treated with sulfapyridine alone (20%).

Another important item in the comparison of serum and sulfapyridine is the speed of recovery. We have shown that crisis occurs more rapidly in patients receiving serum. This is in agreement with Finland's statement, "With the use of sulfapyridine alone, the patients manifest evidence of illness for a considerably longer period. . . . ."

Our results point to the necessity for further study of this problem. We do not believe that any conclusion should be drawn from them for application to the routine treatment of cases of pneumonia, except that both agents are of great value in the treatment of the disease.

Summary. 1. Ninety-six cases of pneumococcus pneumonia treated with serum showed a mortality rate of 16.7%, as compared with a rate of 11% for 136 cases treated with sulfapyridine.

2. Mortality rates were essentially the same for bacteremic cases in the two groups, but were definitely lower in the sulfapyridine group for patients over 40 years and for patients with two or more lobes involved.

3. While both serum and sulfapyridine are of great value in the treatment of pneumonia, we do not believe that conclusions may yet be drawn as to their relative value in its routine treatment.

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CURE OF TYPE XIV PNEUMOCOCCIC MENINGITIS BY SULFAPYRIDINE, CONFIRMED BY AUTOPSY; CASE REPORT.

By Luther L. Terry, M.D.,
INTERNE IN PATHOLOGY, CLEVELAND CITY HOSPITAL,
AND
Edmund E. Beard, M.D.,
SENIOR VISITANT IN MEDICINE, CLEVELAND CITY HOSPITAL; SENIOR CLINICAL INSTRUCTOR IN MEDICINE, SCHOOL OF MEDICINE, WESTERN RESERVE UNIVERSITY, CLEVELAND, OHIO.

(From the Departments of Medicine and Pathology, Western Reserve University and Cleveland City Hospital.)

Several reports of cures of pneumococcic meningitis by sulfapyridine have appeared in the literature since the introduction of this drug by Whitby[9a] in May, 1938. Four such cases have been reported in England.[5,6,9b] Barnett *et al.*[1] recently reported results of treatment of 2 cases, of which 1 (Type V pneumococcus) recovered and the other (Type XIV) died 16 hours after administration of the drug was begun. Long[4] cites the results of Hodes, who treated 4 cases with sulfapyridine. Of these 1 recovered and life seemed to be prolonged in 2. Cutts, Gregory and West[2] successfully treated a case of Type XX pneumococcic meningitis with sulfapyridine and serum.

The case here reported is of especial interest in that not only was there clinical evidence of a cure of the meningitis but, due to death from other causes, we were able to confirm the cure at autopsy and to study the residual changes in the meninges. A further interesting point is the observation that sulfapyridine failed to affect the associated and fatal pneumococcic endocarditis.

Case Report. K. D., a white female aged 62 was admitted to the medical service of this hospital on Jan. 10, 1939. It was impossible to obtain an accurate history from the patient but it was learned from her family that she had apparently been in good health until 5 days prior to admission, when she had contracted a cold. On the day before admission she seemed no worse, but on the following day did not respond in the usual manner, was rigid and unable to walk. The past history was irrelevant except that the patient had been kept in a nursing home for the past several months because of a mental disturbance (probably senile dementia).

Physical examination on admission showed: temperature 39° C., pulse rate 116 and respiratory rate 23 per minute, blood pressure 150 systolic and 90 diastolic. The patient appeared to be seriously ill but answered questions so far as language difficulties would permit. The pupils were very small, regular, equal, and reacted to light. The nose and ears showed no abnormalities. The pharynx was diffusely red and there was considerable mucus present. There was some resistance of the neck on attempts at passive flexion. The chest was symmetrical and expansion was equal on the two sides. Breath sounds were normal and no râles were heard. The heart was enlarged and there was a harsh, blowing systolic murmur audible at the apex. There was no diastolic murmur. The reflexes were physiologic. Babinski and Brudzinski signs were not present.

Five and one-half hours after admission there was definite nuchal rigidity. Lumbar puncture yielded a cloudy fluid under 11 mm. of mercury pressure containing 3000 cells per c.mm., 80% of which were neutrophils. Direct smear showed many Gram-positive diplococci. By the Neufeld-Sabin method the organisms obtained from culture of the spinal fluid were identified as Type XIV pneumococci. Other laboratory findings were: red blood cells, 5,100,000 per c.mm.; hemoglobin, 15 gm. (Sahli); white blood cells, 25,700 per c.mm. The blood Kline was negative. The urine was not abnormal. Blood culture taken on the day of admission showed no growth.

Oral administration of sulfapyridine* was begun at 1.30 P.M. on Jan. 11, 13½ hours after admission. The initial dose was 2 gm. Thereafter 1 gm. was given every 4 hours for 5 doses, then 1 gm. every 6 hours until Jan. 21, when it was discontinued. A total of 35 gm. had been given in 10 days.

Within 48 hours of the beginning of this régime the temperature had reached normal (Fig. 1). The spinal fluid cell count had dropped from 3000 to 180 per c.mm. and on the fifth day was at a virtually normal level, which was thereafter maintained. Smears of every sample of spinal fluid taken

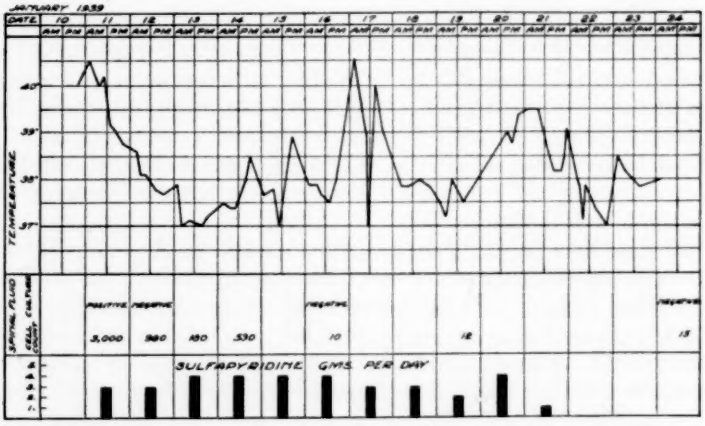

FIG. 1.—Chart showing hospital course, spinal fluid findings and sulfapyridine dosage.

after 24 hours of treatment failed to show organisms. Three of these specimens were cultured and no growth was obtained. Despite these mensurable indications of improvement the patient remained seriously ill. Her stupor continued and she ran an irregular febrile course. Râles were heard in the lung bases on the 7th hospital day. On the 9th hospital day the red blood cell count was 3,600,000, the hemoglobin was 12 gm. (Sahli) and the white blood cell count was 21,500. Sulfapyridine was discontinued on the 11th hospital day, because of the suspicion that it was responsible for the fever, but the patient did not improve. An area of discoloration on the medial aspect of the right thigh was noted early in the morning of the 13th hospital day. Her condition became rapidly worse and she died on Jan. 24, the 15th hospital day.

Autopsy by one of us (L. L. T.) was begun 4 hours after death. The brain weighed 1255 gm. and was of usual appearance. The leptomeninges were thin and transparent and there was no gross evidence of meningitis. The cerebral arteries were the seat of moderate arteriosclerosis but were patent

* The sulfapyridine (Dagenan) used in treatment of this case was furnished by Merck & Co., Rahway, N. J.

FIG. 2.—Section of left frontal cortex and leptomeninges showing the typical appearance (low power magnification).

throughout. The venous sinuses presented the usual appearance and contained no thrombi. Sections for microscopic study were taken from many areas of the base and vertex of the brain (Fig. 2). In these the brain parenchyma showed no lesions. There was an increase in the space between the arachnoid and the pia. This space was filled with a coarse network of collagenous fibers, most of which ran parallel to the leptomeninges. In some areas there were large spaces which possibly represented lymphatic spaces but probably were dilated spaces of the subarachnoid. In the collagenous network there were more cells than commonly present. Some of these cells were stellate, with large vesicular nuclei, and the free edges were apparently continuous with the collagenous fibers. In some instances they contained two nuclei. These cells in all ways resembled the undifferentiated mesenchymal cells of Maximov. In addition, there were a few small lymphocytes and large mononuclear cells present. The latter were phagocytic, and often contained vacuoles and finely granular pigment. The walls of the leptomeningeal vessels were unchanged but for thickening of the adventitia due to marked development of a fine reticular and collagenous network. No exudate was seen.

The heart weighed 300 gm. and was not dilated. The epicardium and myocardium appeared as usual. Upon opening the left atrium a large, lobulated mass was seen to extend into the atrium from its attachment near the base of the aortic leaflet of the mitral valve. The mass, though smooth upon the surface, was granular and friable. It measured 2 cm. in length and was firmly attached to an area of the valve leaflet measuring 1 cm. in diameter. This portion of the leaflet felt firm and fibrotic. There was some thickening of the edges of the mitral leaflets and the chordæ tendineæ were thickened and adherent to one another. There was adherence of the right coronary and non-coronary cusps of the aortic valve at the commissure but there was no evidence of recent inflammation. The tricuspid and pulmonic valves were normal in appearance. The mural endocardium was smooth and transparent throughout, showing no lesions. Microscopic section from that portion of the mitral valve to which the vegetation was attached showed many neutrophil cells enmeshed in a network of fibrin. The deeper portions of this zone were infiltrated by large numbers of young fibroblasts and proliferating capillaries. Bacterial stains revealed many Gram-positive diplococci in the vegetation and deep within the zone of inflammation in the valve leaflet. Other significant anatomic findings were: septic embolus in the right common iliac artery with occlusion of the lumen, recent and remote septic infarcts of the spleen and kidneys, and minimal bronchopneumonia of the right lower lobe. Postmortem culture of the heart's blood and culture of the endocardial vegetation yielded Type XIV pneumococci. Bacterial stains of the iliac embolus and of the infarcts of the kidneys revealed many Gram-positive diplococci.

Comment. This case demonstrates a cure of Type XIV pneumococcic meningitis. The diagnosis was well established by smears and culture of the spinal fluid as well as by the clinical findings. No organisms were seen in direct smears and all cultures were negative 24 hours after sulfapyridine therapy was instituted. Coinciding with these findings there was a drop in the spinal fluid cell count from 3000 to 15 per c.mm. or below. The spinal fluid remained clear and all clinical signs of meningitis disappeared. Autopsy confirmed the absence of meningitis. The only abnormal finding within the cranial cavity was a slight increase in the cellular stroma and the reticular and collagenous network of the leptomeninges. Similar

changes have been described by Gross, Cooper and Lewis[3] in rats which had recovered from experimental pneumococcic meningitis. They also found lesions of the brain parenchyma in about one-half of their animals, but no such lesions were observed in this case. Weil[8] states that comparable lesions are common in old arteriosclerotic brains, in chronic alcoholism, or in renal disease of long standing. Inasmuch as there was moderate sclerosis of the larger cerebral vessels in this case, it is not possible to state whether the findings were due to the cerebral arteriosclerosis or were a result of the recent inflammatory process, or to a combination of the two factors. The cause of death was a pneumococcic pyemia associated with an acute vegetative endocarditis. There was definite evidence of an old rheumatic aortic and mitral valvulitis, but no activity of this process was demonstrable.

The fibrous tissue reaction in the valve leaflet at the base of the endocardial vegetation demonstrates that the lesion of the mitral valve was of longer standing than the meningitis and that the latter process was probably only a result of the pneumococcemia. Ruegesegger[7] has recently pointed out the high incidence of meningitis as a complication of pneumococcic endocarditis. In his series of 19 cases, 13 (86.4%) terminated in meningitis. Of the remaining 6 cases only 1 failed on postmortem study of the meninges or of the spinal fluid to show evidence of meningitis and in this case the endocarditis was confined to the right side of the heart. Despite the fact that in our case the blood culture taken on admission showed no growth, it is probable that there had been a release of pneumococci into the blood stream, at least intermittently. The fact that the infarcts in the spleen and kidneys were of various ages supports this hypothesis.

That sulfapyridine could bring about cure of the meningitis and at the same time fail seriously to affect the endocardial lesion may be more readily understood in the light of Ruegesegger's investigations.[7] He was able to recover viable organisms from pneumococcic vegetations of the endocardium which had been immersed in formalin for as long as 22 months. The therapeutic effectiveness of any blood-borne agent, chemical or immunologic, must be greatly decreased against any organism so protected in an avascular fibrinous mass. Although the drug failed to destroy the focus of infection, the prompt disappearance of the meningitis is significant evidence that sulfapyridine does affect the course of certain pneumococcic infections.

Conclusions. Treatment of a case of Type XIV pneumococcic meningitis associated with pneumococcic endocarditis by the use of sulfapyridine was followed by cure of the meningitis, as judged by clinical criteria as well as by the postmortem examination.

The pneumococcic vegetative endocarditis did not yield to therapy and was responsible for the death of the patient.

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CHLORIDE EXCRETION IN HYPOPITUITARISM WITH REFERENCE TO ADRENOCORTICAL FUNCTION.*

By D. J. Stephens, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE, ROCHESTER, N. Y.

(From the Department of Medicine, University of Rochester School of Medicine and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals.)

In the experimental animal, hypophysectomy is followed by atrophy of the adrenal cortex, which can be prevented or corrected by anterior pituitary transplants or by the administration of extracts containing the adrenotropic principle.[8] In hypopituitarism and Simmonds' disease, atrophy of the adrenal cortex is frequently observed[2,4,7] and in a few such patients death has appeared to occur in Addisonian crisis.[6] Asthenia and hypotension are common symptoms, and pigmentation is occasionally seen in hypophyseal cachexia.[5] Low concentrations of whole blood and serum chloride have been observed in hypopituitarism.[9] Anatomical findings would indicate that chronic adrenal insufficiency occurs in pituitary injury[3] and, if so, one might expect to find disturbances of electrolyte balance in pituitary disease. With this in mind, a study of the chloride excretion of a group of patients with hypopituitarism has been made.

The modification of the chloride depletion test recently described by Cutler, Power and Wilder[1] was used. This procedure consists essentially in the administration of a diet low in sodium and chloride and high in potassium, and the administration of measured quantities of fluid and extra potassium as determined by the weight of the patient. The serum chloride is measured at the beginning and at the end of the test period and the concentration of chloride in the urine is measured. The chloride concentration in a 4-hour specimen of urine collected at the beginning of the third day was found by these investigators to be consistently and significantly higher in patients with Addison's disease as compared with a group of control subjects.

Seven patients with demonstrable lesions of the hypophysis were

* An abstract of this paper was presented at the meeting of the American Society for Clinical Investigation, in Atlantic City, May 1, 1939.

chosen for study. All showed clear evidence of well established hypopituitarism, with complaints of fatigue, weakness, loss of appetite and weight and loss of sexual function. The clinical findings included loss of body, axillary and pubic hair, atrophy of the genitalia, hypotension, decrease in basal metabolic rate and increased glucose tolerance. None of the patients showed evidence of abnormal pigmentation.

During the 52 hours of the test period, the diet described by Cutler, Power and Wilder was given. During the first day of the experimental period free drinking of water was encouraged; on the second day, the fluid intake was adjusted to 40 cc. per kg. and on the third day 20 cc. of fluid per kg. was administered before 11 A.M. On the afternoon of the first day, additional potassium in the form of 42 mg. of potassium citrate per pound of body weight was given. This dose was repeated on the morning of the second day. On the morning of the first day and again on the morning of the third day blood was collected under oil for the determination of serum chloride. On the first and second days the urine was collected from 8 A.M. to 8 A.M.; on the third day, a 4-hour specimen was collected from 8 A.M. to 12 noon. At noon on the third day the test was concluded, the usual hospital diet was resumed and extra amounts of salt were given by mouth for several days.

Non-essential data are omitted from the following case abstracts:

CASE 1.—G.T., a negress, 15 years old, had fallen at the age of 15 months, striking her head. Since that time she had been mentally dull and had suffered from frequent epileptiform seizures. The menses had begun at the age of 12 and had been regular. The general physical examination was essentially negative except for evidences of mental deterioration. The blood pressure was 104 systolic, 58 diastolic. Skin, hair and genitalia were normal. The basal metabolic rate was −3%. The fasting blood sugar was 92 mg. %; whole blood chloride, 492 mg. %. Roentgen-rays of the skull showed evidence of an old fracture in the right parietal region.

In the hope of favorably influencing the epilepsy, on October 15, 1935, craniotomy was done and the hypophysis was cauterized, an attempt being made to destroy completely the gland without injuring the neighborhood structures. Following the operation, there was temporary disturbance of water and salt control, and in temperature regulation. During the week after operation, the whole blood chlorides fell to a consistent level of about 420 mg. %. Within 3 weeks the basal metabolic rate had dropped to −29%. One year after operation there had been some decrease in the number of epileptiform seizures. The weight had decreased from 56.3 to 46 kg. The temperature was 35.7° C., the pulse rate 68. The blood pressure was 70 systolic, 50 diastolic. She was dull and apathetic. The skin was dry and cold. Pubic and axillary hair had disappeared. The menses had ceased abruptly at the time of the operation and the external and internal genitalia had become infantile. The fasting blood sugar was 50 mg. %; whole blood chlorides, 456 mg. %; cholesterol, 300 mg. %; uric acid, 3.6 mg. %. The basal metabolic rate was −33%. The red blood cells numbered 3,600,000; hemoglobin, 12.7 gm. per 100 cc.

In February, 1939, she was re-admitted to the hospital. At this time there had been little change in her clinical condition. She was mentally

dull and apathetic. The blood pressure was 78 systolic, 60 diastolic. The pubic hair was absent. The uterus was infantile. The basal metabolic rate was −47%. The fasting blood sugar was 55 mg. %. During the chloride excretion test there was no significant change in the serum chloride level and the concentration of salt in the urine was found to be within the limits observed in the control subjects (Table 1). She developed no symptoms. About 10 days before the study of chloride excretion was made she had been given 100 units of "Gonadogen" (a gonadotropic preparation of mare serum) without any apparent effect on the sexual organs.

TABLE 1.—CHLORIDES IN HYPOPITUITARISM AND OTHER CONDITIONS.

Patients without evidence of adrenal disease.	Serum chloride–M. Eq. per.L. First day.	Serum chloride–M. Eq. per.L. Third day.	Third day, 4 hr. spec. chloride (as NaCl) mg. per 100 cc.	Symptoms.
Cutler, Powers and Wilder 28 cases		91.5–103 96.5	28–232 89.4	
R. N., Brucellosis	98	98	150	0
J. B., Brucellosis	100	102	40	0
J. C., Anorexia nervosa	...	100	141	0
R. P., Coronary occlusion	102	96	244	0
A. N., Pernicious Anemia	101	100	216	0
M. K., Chronic sinusitis	104	105	100	0
Addison's Disease				
Cutler, Powers and Wilder 7 cases		76.3–94.9 88.2	382–593 489	
Hypopituitarism				
G. T., Hypopituitarism	96	95	171	0
H. S., Pituitary tumor	100	92	427	+
J. D., Pituitary tumor	106	91	494	+
H. B., Pituitary tumor	103	96	364	0
W. S., Pituitary tumor	100	90	620	0
T. B., Pituitary tumor	104	90	503	+
A. B., Pituitary tumor	94	91	690	+

CASE 2.—H.S., a white male, aged 39, was admitted to the hospital September 3, 1937, with complaint of loss of ambition. He had always been overweight and the beard had always been somewhat scanty, requiring shaving only every 2 or 3 days. For 3 years he had noted increasing lassitude, hypersomnia, loss of libido and potentia. He had lost 20 pounds in weight. Necessity for shaving had been reduced to once a week. There had been no headache or visual symptoms. On examination, the temperature, pulse and respirations were normal. The blood pressure in recumbency was 104 systolic, 60 diastolic; standing, 70 systolic, 50 diastolic. He was somewhat obese, with prominent hips and breasts. The skin was pale, smooth and of fine texture. The beard was sparse and inconspicuous. The pubic hair was thin and of feminine distribution. There was no hair in the axillæ, on the trunk or extremities. The testicles were small and soft; the prostate was so small that it could not be identified with certainty. The red blood cells numbered 3,400,000; hemoglobin, 11.6 gm. per 100 cc.; white blood cells, 6000. The fasting blood sugar was 78 mg. %; ½ hour after 50 gm. of glucose by mouth, 126; 1 hr. 80, 2 hrs., 102; 3 hrs., 74; 4 hrs., 78; 5 hrs., 73. Blood cholesterol was 232 mg. %; serum chlorides, 626 mg. %; uric acid, 4.7 mg. %. The basal metabolic rate was −22%. Roentgen-rays of the skull showed evidence of a large pituitary tumor, with enlargement and erosion of the

sella turcica. The visual fields showed bitemporal upper quadrant defect. On October 15, 1937, craniotomy was done and a cystic pituitary tumor was exposed. Chocolate-colored fluid was aspirated and the capsule of the tumor was removed as far as possible. Histologic section showed a cystic pituitary adenoma of the chromophobe type. The post-operative convalescence was uneventful.

In January, 1939, the patient was re-admitted. There had been little change in his symptoms. The beard had become more sparse and axillary hair had disappeared. Blood pressure was 100 systolic, 60 diastolic. The basal metabolic rate was −23%. There had apparently been some decrease in the size of the testicles and further decrease in the size of the prostate which could not be identified. On the third day of the low salt diet the serum chloride decreased to 90 m. eq. and the concentration of salt in the urine was increased (Table 1). During the next day, the patient developed weakness, anorexia, nausea, vomiting, headache and the blood pressure fell to 70 systolic, 40 diastolic. Symptoms were promptly relieved by the intravenous injection of a mixture containing 1000 cc. of water, 10 gm. of sodium chloride, 50 gm. of glucose and 10 cc. of adrenal cortex extract.

Case 3.—J.D., a 48-year-old man, was admitted to the hospital in December, 1938, with complaints of "tired feeling and lack of pep." These symptoms had been noted for several years but had been more marked during recent months. During the past 5 years sexual libido and potentia had been absent. Between 1924 and 1929 he had had severe intermittent headache which had been unexplained. There had been no recent headache or visual symptoms. Significant physical findings included dry but soft, smooth skin, absence of body hair and scant pubic hair. Visual fields were normal. The blood pressure was 88 systolic, 60 diastolic. The prostate was very small. The basal metabolic rate was −14%. The fasting blood sugar was 65 mg. %; ½ hr. after 50 gm. of glucose by mouth, 101; 1 hr., 105; 2 hrs., 91; 3 hrs., 58; 4 hrs., 71. Roentgen-ray examination of the skull showed a greatly enlarged pituitary fossa measuring 3.5 by 2.3 cm., with destruction of the floor of the sella turcica. On the third day of the chloride excretion test he developed weakness, headache, nausea and vomiting. These symptoms were relieved by the intravenous administration of 1000 cc. of physiological saline solution.

Case 4.—W. S., a 52-year-old man, was admitted to the hospital in March, 1939, complaining of weakness, dizziness, fatigue and loss of appetite of about 4 months' duration. There had been some diminution of sexual desire. He had lost several pounds in weight. There had been no headache or visual symptoms. The skin was of normal texture. Hair distribution was normal. The visual fields were full. The blood pressure was 114 systolic, 80 diastolic. The testes were small. The prostate was markedly atrophic. Roentgen-rays of the skull showed enlargement of the sella turcica, with depression of the floor and thinning of the dorsum sella. The basal metabolic rate was −28%. The fasting blood sugar was 77 mg. %; ½ hr. after 50 gm. of glucose by mouth, 111; 1 hr., 124; 2 hrs., 110; 3 hrs., 108; 5 hrs., 69. Although the serum chloride fell to 90 m. eq. on the third day and the concentration of salt in the urine was high (Table 1), he developed no symptoms during the chloride excretion test.

Case 5.—H. B., a 55-year-old man, was admitted to the hospital in 1937, with complaint of headache and failing vision of 1 year's duration. There had been loss of libido since 1934 and body hair had been lost. In December, 1937, a pituitary cyst was evacuated. In February, 1939, he was readmitted. There had been slight improvement in vision but no other change in symptoms. He was chronically ill in appearance. The skin was dry but smooth and of fine texture. The hair was sparse, the eyebrows thin and there was no axillary, body or pubic hair. There was bilateral optic atrophy. Vision

was lost except for the nasal half of the left field. The tongue was large and thick. The blood pressure was 102 systolic, 72 diastolic. The penis was small. Both testicles were small and soft. The prostate could not be identified. The basal metabolic rate was +4%. Blood cholesterol was 227 mg. %. The fasting blood sugar was 74 mg. %; ½ hr. after 50 gm. of glucose by mouth, 116; 1 hr., 134; 2 hrs., 69; 3 hrs., 78; 5 hrs., 81. Roentgen-ray of the skull showed marked enlargement of the pituitary fossa. The patient developed no symptoms during or after the chloride excretion test.

CASE 6.—T. B., a 49-year-old-man, was admitted to the hospital January 29, 1939. In 1934 he had had craniotomy and partial removal of a chromophobe adenoma of the pituitary because of visual symptoms. After operation vision had improved but during the past year the vision had again been failing and he had been having intermittent headache and occasional nausea and vomiting. The appetite had been poor and he had lost weight. There had been increasing sensitivity to cold and the skin had been dry. Axillary and body hair had disappeared and the pubic hair had become very scant. For several years there had been gradual decrease in sexual function; for 18 months there had been complete loss of sexual libido and potentia. He had noticed that the penis had become small and that the testicles had become small and soft. On examination, he was pale and chronically ill in appearance. He was somewhat overweight. The skin was dry, soft and smooth. The eyebrows and beard were thin. There was no axillary or body hair. The pubic hair was very sparse. He was mentally dull and irritable. The right pupil did not react to light. There was bilateral optic atrophy, more marked on the right. Vision was lost except for the nasal half of the left field. The blood pressure was 90 systolic, 60 diastolic in recumbency; 72 systolic, 58 diastolic sitting. The testes were small and soft, each about the size of a robin's egg. The prostate was very small, flat and vaguely outlined. The basal metabolic rate was − 37%. The blood cholesterol was 480 mg. %. The fasting blood sugar was 86 mg. %; ½ hr. after 50 gm. of glucose by mouth, 73; 1 hr., 75; 2 hrs., 64; 5 hrs., 95. Roentgen-rays of the skull showed marked enlargement of the pituitary fossa, with thinning and depression of the floor, thinning of the dorsum sella to paper thickness and erosion of the posterior clinoids. On the third day of the chloride excretion test he developed headache, weakness, irritability, nausea and vomiting. These were relieved by the intravenous administration of sodium chloride, glucose and adrenal cortex extract. During the next few days he was given extra salt by mouth (Chart 1). The chloride excretion test was then repeated with the daily administration of 5 cc. of adrenal cortex extract intramuscularly. The changes in the serum chloride and urine chloride concentration were modified and he failed to develop symptoms.

CASE 7.—A. B., a 57-year-old man was admitted to the hospital in January, 1938, with history of 2 years' duration of fatigue, weakness and weight loss. He had lost 60 pounds during the first 8 months of the illness and had developed marked anorexia, loss of hair, dryness of the skin, loss of sexual desire and increased sensitivity to cold. Between June, 1936, and September, 1937, he took injections of various anterior pituitary extracts; during this time his appetite improved and he gained about 45 pounds in weight. The other symptoms remained about the same. Between September, 1937, and January, 1938, he had been without treatment, had lost 20 pounds and complained of increased fatigue, weakness and anorexia. On examination, he was poorly nourished and appeared chronically ill. The skin was dry, smooth and of fine texture. The hair was thin and sparse. The blood pressure was 85 systolic, 58 diastolic. The weight was 70.4 kg. Roentgen-ray of the skull showed marked enlargement of the pituitary fossa, with thinning of the floor and of the dorsum sella. The basal metabolic rate was −30%. Blood cholesterol was 250 mg. %. The fasting blood sugar

was 71 mg. %; ½ hr. after 50 gm. of glucose by mouth, 180; 1 hr., 125; 2 hrs., 61; 3 hrs., 62.

In January, 1939, he was readmitted. During the past year he had been given intramuscular injections of an anterior pituitary extract 3 times weekly and had taken 2 grains of dessicated thyroid daily. In spite of such treatment he had lost 40 pounds in weight and had developed extreme anorexia, marked weakness and fatigue. There was absence of sexual desire and potency. He was abnormally sensitive to cold and had ceased to perspire. He had noted decrease in size of testes and penis. On examination, he was apathetic, depressed and irritable. He appeared emaciated and chronically ill. Weight was 52 kg. The skin was dry, and smooth. The beard was sparse. There was no axillary or body hair. There were a few fine, long hairs on the arms. The pubic hair was scant and of feminine

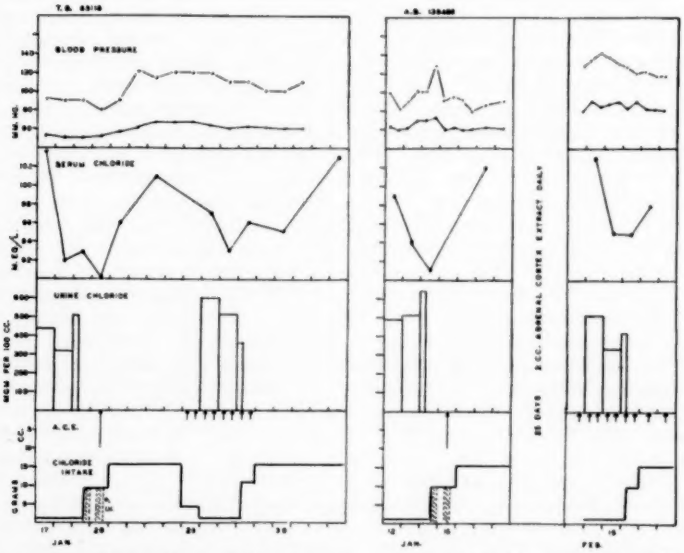

CHART 1.—Observations of blood pressure, serum chloride and urine chloride concentration in 2 patients with hypopituitarism before and after the administration of sodium chloride and adrenal cortex extract (A. C. E.)

distribution. The blood pressure was 108 systolic, 60 diastolic in recumbency; 92 systolic, 64 diastolic standing. The penis was small. The testes were atrophic, measuring about 2 by 4 cm. The prostate was very small and flat. The basal metabolic rate was −42%. The fasting blood sugar was 62 mg. %; ½ hr., after 50 gm. of glucose by mouth, 159; 1 hr., 102; 2 hrs., 50; 3 hrs., 54. On the third day of the chloride excretion test he became nauseated, vomited 3 times and was weak, apprehensive and exhausted. These symptoms disappeared after the intravenous administration of fluid, salt, glucose and adrenal cortex extract.

During the following 25 days he was given 2 cc. of adrenal cortex extract and took 10 gm. of extra salt daily. He returned on February 14th and reported increased appetite, increase in strength and an improved mental outlook. The physical findings were essentially as before except that the blood pressure was 130 systolic, 84 diastolic. The basal metabolic rate had

increased to −11% (2 determinations). The weight was 53 kg. The second chloride excretion test showed modifications in the serum and urine choride changes (Chart 1). This time he developed no symptoms.

He continued to take 1 cc. of adrenal cortex extract intramuscularly and 10 gm. of extra salt by mouth daily. On April 11, 1939, he weighed 66 kg., having gained 31 pounds. He had developed a ravenous appetite, had improved markedly in strength and endurance and was enthusiastic, cheerful and encouraged in contrast to the previous apathy and depression. The systolic blood pressure had increased to between 140 and 160, the diastolic to between 80 and 88.

Discussion. Table 1 shows a summary of the observations of serum chloride and urine chloride concentration in the patients with hypopituitarism and in a group of control subjects without evidence of endocrine disease. In the control group, there was no significant change in the serum chloride levels and the excretion of salt in the 4-hour specimens collected at the beginning of the third day was in the range observed by Cutler, Power and Wilder[1] in a larger group of similar subjects. The first patient with hypopituitarism, in whom the hypophysis had been removed some years before, showed a normal response to the test. It is possible that the results may have been modified by the recent administration of Gonadogen. Each of the other 6 patients with hypopituitarism showed significant decreases in serum chloride during the period of chloride depletion and a high concentration of salt in the 4-hour third day urine specimen in the range found by Cutler, Power and Wilder to be characteristic of adrenocortical insufficiency. Four of these 6 patients developed symptoms suggesting those of the Addisonian crisis, associated with decrease in the serum chloride level. These symptoms were promptly relieved by the intravenous administration of sodium chloride, glucose and adrenal cortex extract. In 4 patients in whom the serum sodium was determined it was found to be decreased on the third day of salt depletion. No significant changes in the non-protein nitrogen or the carbon dioxide combining power of the blood were observed.

In 2 of the patients who had developed symptoms the test was repeated after the administration of salt and adrenal cortex extract. During the first period of salt depletion 1 patient (T. B.) had developed symptoms on the third day which were relieved by the administration of salt and adrenal cortex extract. After several days of high sodium chloride intake, the test was repeated with the daily administration of 5 cc. of adrenal cortex extract. The results were modified in that the serum chloride level fell to 95 rather than to 90 m. eq. and the concentration of salt was lower than in the first experiment, but still in the abnormal range. This time he developed no symptoms. The second patient (A. B.) developed symptoms on the third day of the test with a serum chloride level of 91 m. eq. He left the hospital and for 25 days took extra salt and adrenal cortex extract daily. Repetition of the test resulted in a modifica-

tion of the serum and urine chloride changes (Chart 1) and he developed no symptoms. The continued administration of salt and adrenal cortex extract resulted in striking clinical improvement and gain in weight. The doses of adrenal cortex extract which were used were so small that one suspects that the modifications in chloride excretion and the striking clinical improvement in the second patient may have been due to the extra salt intake as much as to any specific effect of adrenocortical substance.

These observations appear to confirm the impression that limitation of adrenal function occurs in hypopituitarism and suggest that this factor should be taken into consideration in the treatment of such patients and in the differential diagnosis of hypopituitarism and Simmonds' disease. There may, however, be other factors in pituitary disease which conceivably might influence the electrolyte balance. For example, Thorn and Engle[10] have shown that the sex hormones, progesterone, testosterone and the œstrogens, as well as the adrenocortical principle may cause retention of electrolytes in the normal and adrenalectomized animal and in patients with Addison's disease. Although experimentally the sex hormones are effective only in relatively large doses, the question is raised as to whether the changes observed in this group of patients may have been associated with secondary gonadal as well as adrenal insufficiency. In none of the patients with hypopituitarism was there evidence of pulmonary or renal disease or of involvement of the hypothalamus or posterior pituitary which might have influenced salt excretion.

Summary. Six of 7 patients with clinical hypopituitarism, when studied under standard conditions of salt depletion, showed increased concentrations of chloride in the urine similar to that which has been found to be characteristic of adrenocortical insufficiency.

Four of the 6 patients developed symptoms suggesting those of Addisonian crisis. These symptoms were promptly relieved by the intravenous administration of sodium chloride, glucose and adrenal cortex extract.

In 2 patients symptoms failed to occur and chloride excretion was favorably modified after the administration of sodium chloride and adrenal cortex extract. One patient experienced striking clinical improvement during the administration of sodium chloride and adrenal cortex extract.

These observations are interpreted as confirmatory evidence of the occurrence of chronic adrenocortical insufficiency in clinical hypopituitarism, presumably secondary to withdrawal of the adrenotropic anterior pituitary principle.

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THE AMOUNT OF LYMPHOID TISSUE OF THE HUMAN APPENDIX AND ITS WEIGHT AT DIFFERENT AGE PERIODS.

By Joseph M. S. Hwang, B.S., M.D.,*

and

Edward B. Krumbhaar, M.D., Ph.D.,

Philadelphia, Pa.

(From the Department of Pathology, Graduate School of Medicine, University of Pennsylvania.)

This presentation is part of a general study of the morphologic changes of human lymphatic tissue at different ages, an investigation stimulated by a consideration of the problems in ageing, in the book of that name edited by E. V. Cowdry.[6] Though the lymphatic tissue taken as a unit is probably one of the largest organs of the body, being said to be even larger than the liver, its widely scattered distribution and rapid response to environmental change make quantitative studies difficult. For instance, while it is accepted that the various lymphatic tissues of the human body begin to retrogress at different periods in the life cycle, actual figures on the subject are extremely meager. As an example of retrogression differences, the thymus, one of the components of this complicated system, has already begun its involutionary changes before sexual maturity and while the lympathic tissue elsewhere is still developing toward a maximum. Having completed a study in the spleen, which analyzed the weights of 4000 supposedly normal spleens and the amount of splenic lymphatic tissue in 300 violent deaths at different ages,[5] we now offer the results of a similar study on the appendix. Difficulties in obtaining "normal" material and the time and the labor involved in securing the necessary data are apparently the main reason that these problems have not already been adequately studied.

Muthmann's study of the appendix[7] led him to the view that regression starts early in childhood, while Berry and Lack[3] and

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Corner[4] found that it began later in life. Stefanelli[8] claimed that normally no lymphatic follicles could be found in the appendix after the age of 75, while the latest study of Bernardo-Comel[2] found, as we have also (Chart 1), that they persisted throughout life. Because of such sparse and yet divergent experiences, and the differences in methods and material, much of it being from diseased organs or from autopsies after death from disease, a more rigidly controlled investigation seemed desirable.

Methods. Human appendices from 300 cases of sudden, violent deaths, excluding individuals who were found either from the history or postmortem examination to have any recognizable disease or to have survived more than 10 hours after the violence, were studied by the methods outlined in the spleen study. In this material, chief causes of death were automobile accidents and gun-shot wounds (excluding those of the abdomen); except for a few cases of carbon monoxide poisoning, all poison cases were excluded. Each appendix was placed in formalin with a portion of the cecum and the mesoappendix attached, ensuring that the whole appendix had been received. The cecum and mesoappendix were removed before the appendix was weighed. This affords weight comparisons between the appendices studied here, but not between these and unfixed appendices, as organ weights change considerably during and after formalin fixation. Blocks were taken from each appendix at three different levels (proximal, middle and distal). All of these blocks included the lumen. The blocks were embedded in paraffin, sections cut at approximately 6 μ in thickness, stained with Harris' hematoxylin and eosin, and low power fields (8.6×) projected for outlining, as in the spleen study. Three outlines were traced: the walls of the appendices, their included lymphatic follicles, and the "pale centers," if present; the areas of the total cross section, the lymphatic follicles, and the pale centers were afterwards measured with the planimeter. Further details of the method can be found in the spleen article.

The percentage of lymphatic tissue as a whole in the section is termed the "gross" percentage and that from which the "pale centers" had been deducted, the "net." The weight of the lymphatic tissue was calculated by multiplying the weight of the organ by the percentage of lymphatic tissue found. The marginal zone (*Aussenrandzone*) encountered in the splenic series was not met with in this series, and the traced areas were found to be sharply defined. Beyond the follicles the mucosal zone contained only a few isolated lymphocytes, so that the estimation of the follicular areas as representing the total lymphatic tissue was less open to subjective error than in the case of the spleen study. For comparison, in 10 cases sections were also made longitudinally, or parallel to the long axis of the appendix, as a control for variations not covered by this procedure, and in 6 cases cross sections were made at various levels between the proximal and distal sections. We found that the percentages obtained in these controls were not significantly different from those found in the three standard sections described above. The larger total amount of lymphatic tissue obtainable in the longitudinal sections would have constituted preferable material, had it not been for the unavoidable damage to the mucosa while spreading the fixed

specimen; thus, of course, vitiating the percentages obtained. In about 90% of the specimens received, the lumen contained yellowish fecal material; most of these appendices had a smaller external circumference at the middle portion than at either the proximal or the distal ends.

Each specimen was studied microscopically before projection for signs of acute or chronic inflammation, fibrosis, and other definite lesions. Where any such lesions were present, the material was discarded (more than 70 appendices beyond the 300 analyzed). Those that had many "pale centers" were scrutinized for disease with

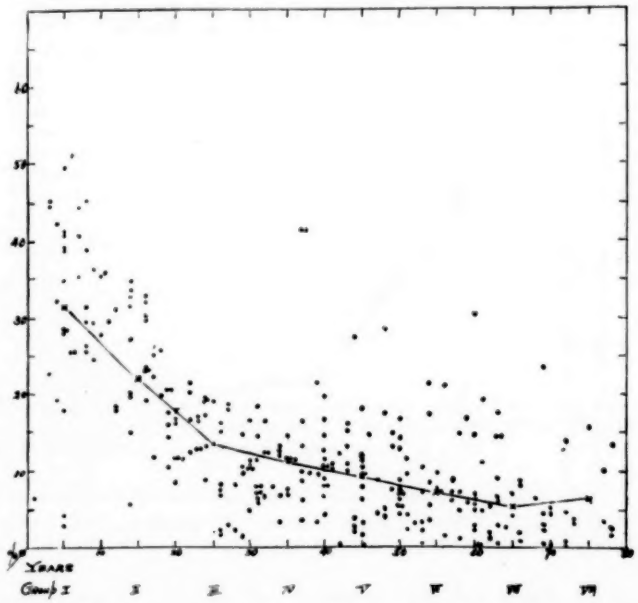

CHART 1.—"Gross" percentage of lymphatic tissue of the human appendix at different ages in 300 cases of violent deaths. Dots indicate individual percentages, the curve indicates the mean for each decade.

special care, though it was eventually found that they exhibited lesions in no greater numbers than did the rest of the material.

Results. Fortunately the material was distributed fairly evenly among the different age groups, with the exception of cases in the first year of life and those over 80. Except for these and the 71–80 age group (Group VIII), in which the cases numbered 14, all groups contained not less than 30 cases each.

The "gross" percentage of lymphatic tissue, as shown by Charts 1 and 2, starts at a maximum in the first decade. The single case less than one year old, showed a small percentage of lymphatic tissue,

just as in the splenic series at that age; it is probable that a larger number of cases at this age would show a low average percentage in the first year of life. The lymphatic percentage drops sharply in the second and third groups, and then very slowly though steadily until the seventh group, where a small elevation of the curve is noticed. A difference between the "gross" and "net" percentages of lymphatic tissue (*i. e.*, due to existence of "pale centers"), and also between the "gross" and "net" weights was readily observable only in the first two groups (1–10 and 11–20 years).

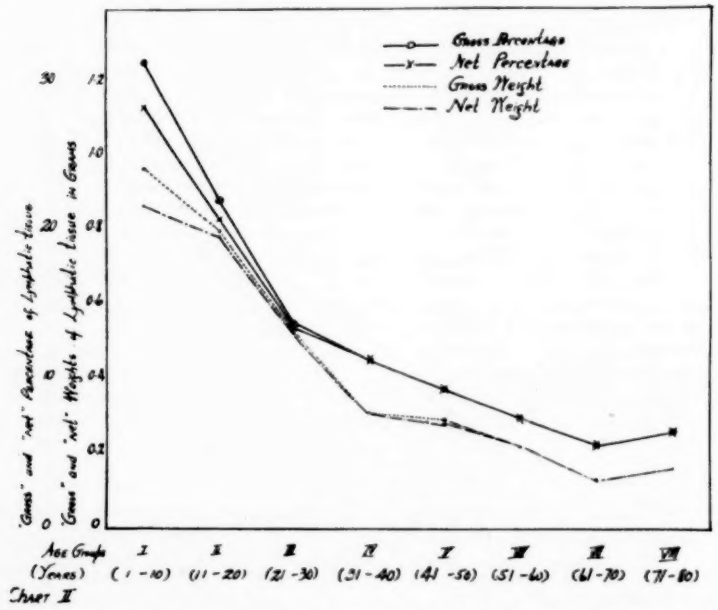

CHART 2.—"Gross" and "net" percentages and calculated weights of lymphatic tissue in the appendix at different ages.

It is also of interest to note that a number of appendices over 40 years showed considerable fatty deposits in the submucosa. These we included in our series, though their presence, of course, influenced both the mean percentages and absolute weights. However, this may be a phenomenon of the actual ageing process of the appendix and thus of its included lymphatic tissue.

About 3% of our specimens showed more or less obliteration of the lumen. These 9 appendices all fell in the last three age groups. In spite of the obliterations, characterized by thin strands of fibrous tissue with included fatty deposits, no other abnormalities could be found, though they always showed a minimum amount of lymphatic tissue.

TABLE 1.—LYMPHATIC TISSUE OF APPENDIX AT DIFFERENT AGES IN 300 CASES OF VIOLENT DEATH.

Group.	Absolute weight.			Percentage.		
	No.	Mean.*	Standard error of mean.	No.	Mean.	Standard error of mean.
O (0–1 yr.)	1	0.21		1	12.1	
I (1–10 yrs.)						
"Gross"	36	0.97	0.05	36	31.4	1.9
"Net"	36	0.87	0.04	36	28.4	1.65
II (11–20 yrs.)						
"Gross"	39	0.80	0.075	39	22.1	1.2
"Net"	39	0.79	0.075	39	20.9	1.2
III (21–30 yrs.)						
"Gross"	40	0.53	0.070	40	13.7	1.0
"Net"	40	0.52	0.070	40	13.5	1.0
IV (31–40 yrs.)						
"Gross"	46	0.31	0.03	46	11.3	0.8
"Net"	46	0.31	0.03	46	11.3	0.8
V (41–50 yrs.)						
"Gross"	45	0.29	0.03	48	9.4	0.8
"Net"	45	0.28	0.025	48	9.3	0.7
VI (51–60 yrs.)						
"Gross"	42	0.22	0.03	42	7.4	1.0
"Net"	42	0.22	0.03	42	7.4	1.0
VII (61–70 yrs.)						
"Gross"	32	0.13	0.02	32	5.5	0.85
"Net"	32	0.13	0.02	30	5.5	0.85
VIII (71–80 yrs.)						
"Gross"	14	0.16	0.04	14	6.5	1.35
"Net"	14	0.16	0.04	14	6.5	1.35
IX (81–90 yrs.)						
"Gross"	2	0.48		2	21.3	

* The mean absolute weight in each group was obtained from absolute weights calculated for each individual, rather than by multiplying the group means of appendix weights by the lymphatic percentages.

The single appendix from an infant less than one year old had definitely less lymphatic tissue than the other appendices of the first decade. The two specimens from persons over 80 happened to have more lymphatic tissue than those of the previous decade (see statistical analysis).

Analysis according to sex revealed that the percentage and absolute weight, both the "gross" and "net," were significantly lower in the female than in the male (Table 2).

The weight of the appendix (Table 3, Chart 3) reached its maximum in the second age group (11–20 years), and thereafter receded gradually and steadily. Tables 1 and 3 show that the calculated gross lymphatic weight dropped 17% from Group I to Group II, while the total weight of the appendix showed a rise of 45%; from Group II to Group III the lymphatic tissue revealed a drop of 34% while the appendiceal weight attained a drop of only 13%; and from Group III to Group IV, a 41% drop was found in the lymphatic weight, but only a 10% drop in the weight of the appendix. From Group V on, the loss in both the lymphatic and appendiceal weights runs practically parallel.

TABLE 2.—"GROSS" AND "NET" LYMPHATIC WEIGHTS AND PERCENTAGES ANALYZED ACCORDING TO AGE AND SEX.

	No. of cases.			Lymphatic weights.		Lymphatic percentages.	
Group.	Male.	Female.		Male.	Female.	Male.	Female.
I	26	10	"Gross"	1.01	0.88	32.9	27.3
			"Net"	0.91	0.80	30.6	21.8
II	32	7	"Gross"	0.86	0.57	22.6	20.3
			"Net"	0.84	0.55	21.4	19.5
III	31	9	"Gross"	0.54	0.49	13.7	12.7
			"Net"	0.53	0.49	13.5	12.5
IV	39	7	"Gross"	0.33	0.23	11.5	10.3
			"Net"	0.33	0.23	11.5	10.3
V	42	6	"Gross"	0.30	0.24	9.2	11.2
			"Net"	0.29	0.23	9.1	11.1
VI	34	8	"Gross"	0.23	0.27	7.1	8.6
			"Net"	0.23	0.27	7.1	8.6
VII	26	6	"Gross"	0.14	0.10	5.6	5.2
			"Net"	0.14	0.10	5.6	5.2
VIII	13	1	"Gross"	0.17	0.05	6.8	3.4

Statistical Analysis. The peak of the curves of both percentage and calculated absolute weight of the lymphatic tissue is in the 1–10 year old group (Table 1, Chart 2).

In the curves of the absolute lymphatic weights, both "gross" and "net," in Groups I to IV (Table 1, Chart 2) the means are both steadily and significantly different from each other (*i. e.*, in each case the difference of the means is greater than twice the standard error of the mean).

The curve of "gross" lymphatic weights for Groups I to IV inclusive is sharply down grade, with a regression coefficient of -0.23. From Group IV to Group VIII, the slope is more gradually downhill —but definitely so—with a regression coefficient of -0.175 and a standard error of the regression coefficient of 0.02. As the value of -0.075 is about four times 0.02, the slope is definitely downgrade, the regression coefficient of a horizontal line being 0 (Table 1).

The values for the 2 cases in Group IX (not on chart) are much greater and about at the limit of significant difference from those of Group VIII. However, this cannot be taken as indicating a tendency of lymphatic tissue to increase at this age period, unless confirmed by a much larger number of cases. The rise in Group VIII is not statistically significant. The lessened downward tendency in Group V is of interest as occurring at about the same age as a more definite hump in the curve of splenic lymphatic tissue.

TABLE 3.—WEIGHTS OF APPENDICES AT DIFFERENT AGES.

Group.	Gm. (fixed in formalin).
I	2.57
II	3.74
III	3.23
IV	2.89
V	2.73
VI	2.54
VII	2.05
VIII	2.04

The curve of the "gross" percentages of lymphatic tissue is much the same as that of the absolute weights, but the sharper decline stops one group earlier, at Group III rather than Group IV. Therefore, the regression coefficient of the first three groups is -8.8; of Groups III–VIII is -1.45 with a standard error of the coefficient of 0.28.

The curves of the "net" percentages (*i. e.*, excluding the "pale centers") are much the same as those of the "gross" percentages. The only difference is a considerably and significantly lower value in Group I, and a smaller difference in Group II.

Discussion. In the present series, except for the cases in the first few months of life and those over 70 years of age, there are about the same number of cases in each age group, and enough for adequate statistical study. We recognize a handicap that seems insurmountable in such a study, namely that in an uncertain number of cases both total weight and percentage of lymphatic tissue may have been permanently modified by the effects of previous inflammation without leaving telltale signs. The results have proven, however, to be more consistent than in the spleen study, with a corresponding increase in significance. There is apparently a steady decrease in the lymphatic tissue of the appendix throughout life, after the maximum has been reached in the first age group. As in the case of the spleen material, the lymphatic tissue is apparently small in the first few months of life, though we have not had adequate material to be certain on this point.

Subtraction of the "net" from the "gross" figures on the lymphatic tissue gives an estimate of the amount of space occupied by the "pale centers." Only in the first decade (to a lesser extent in the second decade) do these play any noticeable rôle. The interpretation of these observations depends on what these "pale centers" are taken to represent. As indicated in our previous treatment of this subject, we believe that they may under different circumstances either serve as true lymphoblastic tissue, so-called "germinal centers," or more frequently as "reaction centers" made up of elements of the reticulo-endothelial system. From this point of view, the "pale centers" in the first age group are taken to be lymphoblastic, at a time when the young lymphatic tissue is actively hyperplastic. The absence of the "pale centers" in later life (*i. e.*, when they are regarded as usually being "reaction centers,") is taken as a further indication of the normal quality of the material (*i. e.*, absence of inflammatory processes in the body at the time of the violent death).

The gross weight of the 300 appendices also showed a steady decline after an initial increase from the first to the second decade of life. In the "spot" chart of individual appendix weights (Chart 3) it will be seen that there is a marked increase in appendiceal weight with the fourteenth year, an indication in accord with the observations of other authors, and also with our spleen material (see the "spot"

chart of that study), that human lymphatic organs tend to increase markedly in weight at the time of puberty. Analysis of the decline in total appendix weight after puberty shows that it is not as marked as that of the lymphatic tissue within the appendix in the same age periods.

The maximum weight of the organ and of its lymphatic tissue content (in the first decade of life, when taken by decades) appears to be reached earlier than in the other lymphatic tissues of the body, excepting the thymus. This, however, is not altogether incompatible with the generalization that infections tend to be most prevalent

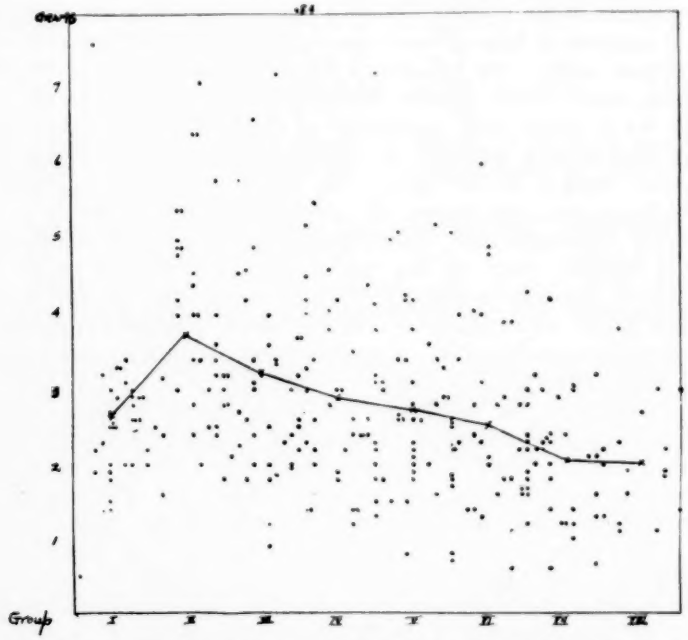

CHART 3.—The weights of the formalin-fixed appendices at different ages in the 300 cases. Dots indicate individual weights, the curve indicates the mean for each decade.

at ages when lymphatic tissue is abundant. Appendicitis is rare in infancy when appendiceal lymphatic tissue appears to be scanty; it is not infrequent in the prepubertal period, and, according to Ashhurst[1], is commonest from 10 to 30 years. When the other factors that contribute to appendicitis are taken into account, this will be seen to constitute a fairly good correlation. Its significance is quite another matter; it is difficult to understand why the individual should be most susceptible at a time when a system that is accepted as being a defense mechanism is at or near its maximum. This discrepancy is even more difficult to understand in the case of the appendix than in that of the tonsils, where the persistence of foci

of infection and distortion from previous attacks undoubtedly play a greater rôle in frequent attacks than they do in the appendix.

Analyzed according to sex, the calculated weight of the lymphatic tissue in the appendix is significantly less in females, though this observation is weakened by the smaller number (about 25%) of females in the series and by the absence of data on the total body weights. Up to the forty-first year, the lymphatic percentages are also less in the female than in the male. Analyzed according to sex, the gross weights of our 4000 spleens are in accord with the appendix figures, in that the female spleens are lighter than the male spleens, and the difference in spleen weights is greater than that of the total body weights of the two sexes. The reason for these differences is not apparent.

We were especially interested in comparing the amount of lymphatic tissue in the appendix in the later decades of life. In our spleen studies, we found suggestive increases (or a tendency to level off the falling curve) in the age periods between 50 and 65 years. The present study, however, fails to show such a change (the slight leveling from 41 to 50 years being insignificant); and thus gives no support to the suggestion raised by our spleen material and occasionally found in the literature, to the effect that there is a tendency for the lymphatic tissue to show a secondary increase in later life.

Summary and Conclusions. 1. The amount of lymphatic tissue in the human appendix has been studied in 300 persons dying violent deaths, and analyzed according to eight age groups and to sex.

2. The percentage of the lymphatic tissue and its calculated weight were found to be greatest in the first age group (1 to 10 years) and to diminish fairly steadily throughout life. The later secondary rise found in our spleen material was not observed.

3. The appendix attains its maximum weight in the second decade, about the age of puberty, and then decreases in weight throughout life, but less markedly than does its lymphatic tissue.

4. The female appendix apparently contains less lymphatic tissue than the male throughout life.

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FURTHER STUDIES OF THE INTRACUTANEOUS METHOD OF TYPHOID VACCINATION.*

By Louis Tuft, M.D.,

ASSOCIATE IN IMMUNOLOGY, TEMPLE UNIVERSITY SCHOOL OF MEDICINE; CHIEF OF CLINIC OF ALLERGY AND APPLIED IMMUNOLOGY, TEMPLE UNIVERSITY HOSPITAL, PHILADELPHIA, PA.

(From the Clinic of Allergy and Applied Immunology, Temple University Hospital and Medical School.)

In 1932, Yagle, Rogers and the author[10] reported the results of a comparative study of the antibody response after the administration of a mixed typhoid vaccine by the intracutaneous, subcutaneous, intramuscular, intravenous and oral routes. This study indicated that insofar as agglutinins and complement-fixing antibodies were concerned the response was uniformly better and more persistent after local injection. This was particularly true of the intracutaneous route, even though the total dose by this method was only one-fifth of that given subcutaneously or intramuscularly. These observations helped to substantiate the fact as indicated by other experiments and by a review of the literature which the author reported in 1931,[9a] that the skin was an extremely important immunologic organ and that it participates very actively in antibody production. This conception of the skin as an active agent in immune antibody production as well as our demonstration of the marked antibody production after intracutaneous injection of typhoid vaccine suggested the utilization of this route of administration in routine typhoid immunization. A study of the response of more than 100 individuals who were given four doses (0.05, 0.1, 0.15 and 0.2 cc.) of typhoid vaccine intracutaneously at weekly intervals indicated that this method of vaccination gave a satisfactory immunologic response; also that the injections were accompanied by considerably less local reaction and by almost complete elimination of those annoying constitutional symptoms that follow other methods of administration. Because of these advantages, it was suggested that the intracutaneous method be used in typhoid immunization instead of the subcutaneous or intramuscular routes.[9b]

Subsequent to the publication of these studies, additional verification of the efficacy of the intracutaneous route of immunization was furnished by its employment for purposes of active immunization in the lower animal as, for example, with pneumococcus vaccine. Likewise, Kern and his co-workers, encouraged by our results with typhoid vaccine, successfully utilized the intracutaneous method in active immunization against diphtheria with diphtheria toxoid[5] and against scarlet fever with scarlet fever streptococcus toxin.[6] They

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were able to show that positive reactors could be rendered Schick- and Dick-negative by the intracutaneous administration of much smaller doses; furthermore, there occurred a marked reduction or almost complete elimination of those discomforting and at times severe local and constitutional reactions that were so frequent, especially in adults.

Prior to the time of our original publication, most of the immunologic studies in typhoid infection or after typhoid vaccination usually were concerned with the agglutinin response as a whole without attempting to differentiate the type. In recent years, more attention has been given to their differentiation as originally proposed by Felix,[3] into a species-specific somatic or "O" agglutinin and a type-specific flagellar or "H" agglutinin. Felix and others[1,4] have shown that the O agglutinin appears earlier and in higher titer in frank typhoid infection than the flagellar or H agglutinin and seems to indicate a more favorable prognosis. The H agglutinin, on the other hand, was produced in higher titer than the O antibody in vaccinated individuals. Contrary to the original conclusion of Felix, that O agglutinins do not appear in vaccinated individuals, observations, particularly by Dulaney and his co-workers,[2] and by Perry,[7] have shown that these antibodies do appear in vaccinated individuals. Perry's report is of further interest to the present study because he showed that the H and O agglutinins appeared in equally high titers and that these titers were the same in the group of individuals given the vaccine intracutaneously in doses of 0.05, 0.1 and 0.1 cc. as in those given the vaccine subcutaneously in doses of 0.5, 0.8 and 1 cc. at weekly intervals; also, one dose of vaccine (either 0.1 cc. intracutaneously or 1 cc. subcutaneously) given to previously vaccinated individuals was sufficient to increase the titer of both H and O agglutinins to a point beyond that of the non-vaccinated group; also, that these persisted in the blood for as long as a year in more of these individuals than in the non-vaccinated group. Furthermore, Perry confirmed my original observation that the intracutaneous injection of vaccine rarely resulted in a systemic reaction, which was in contrast to that of the subcutaneously injected individuals.

One of the difficulties in estimating the effectiveness of typhoid immunization from a laboratory standpoint is the necessity for depending entirely upon antibody response in vaccinated individuals. This is unsatisfactory since the presence of agglutinins which are taken as the usual indicator does not persist in adequate amount for more than 3 to 6 months and in most instances are absent from the blood within a year. This does not mean, of course, that such an individual is not immune. Experience with vaccinated individuals in epidemics and especially in the army has indicated that actively acquired immunity of this type may persist for a much longer time. It is neither feasible nor desirable, of course,

to test the efficacy of vaccination in civilian life by direct exposure to infection: for this reason, any test which will shed some light on the protective power of the blood of such individuals would be more helpful. This has been furnished to some extent by the use of the mouse-protection test, employed originally for other organisms, but adapted for the typhoid bacilli by Siler.[8] In this test the serum of the patient is injected intraperitoneally into mice followed in ½ hour by measured amounts of the causative organisms, using as controls mice which received only the organisms. If the serum prevents death of the mice from infection in certain dosage in comparison to the controls, it is taken as an indication that protective antibodies are present.

In spite of the seemingly obvious advantages of the intracutaneous method of typhoid immunization as well as the definite evidence of satisfactory immunologic response, this method has not as yet been generally adopted. Before making further recommendations, it was decided to carry out studies designed to re-check our original observations as to the immunologic response to intracutaneous typhoid vaccination with additional observations as to the effect not only upon the H agglutinins but also upon the O agglutinins and upon the bacteriolytic power as measured by mouse-protection tests. Accordingly, the following studies were carried out:

Procedure. 1. A group of 45 individuals who had never been immunized previously against typhoid were injected subcutaneously at weekly intervals with 0.5 cc., 1 cc., and 1 cc., respectively, of typhoid vaccine No. 97513 containing 2000 million *E. typhosus* per cubic centimeter. A second group of 56 individuals who likewise had never been immunized previously against typhoid were injected intracutaneously at weekly intervals with 0.1 cc., 0.15 cc. and 0.2 cc. of the same vaccine. Record was made of any marked local reaction or any constitutional symptoms occurring in either group. Three weeks after the last dose had been given blood was obtained and the serum examined for both H and O agglutinins. The 3-week interval was chosen because our previous studies as well as those of others had shown that a satisfactory agglutinin titer could be expected at about that period.

The examination of the sera for H and O agglutinin were conducted in the routine manner now being employed by the Pennsylvania State Health Laboratories for the H agglutinins. A standard Dreyer antigen of a Grinnel strain was employed, the tests incubated at 50° C. for 18 to 20 hours and read immediately after removal from the incubator. The highest dilution showing definite agglutination was taken as the titer. The procedure for the O agglutinin was similar except that the antigen was prepared by alcoholic extraction of a No. 305 non-motile strain. The readings were also made in the same manner.

2. Encouraged by the agglutinin response secured by subcutaneous and intracutaneous treatment with typhoid bacterin No. 97513, we proceeded with the treatment of two groups with a sensitized typhoid vaccine No. 26063, also containing 2000 million *E. typhosus* per cubic centimeter. The individuals in these groups had not previously received typhoid immunization. Bleedings were made before treatment and again 3 weeks after treatment. One group, designated as Group 1 and consisting of 19 members, received 0.5 cc., 1 cc., and 1 cc. at weekly intervals subcutaneously. Another group, designated as Group 2 and consisting of 9 members, received 0.1 cc., 0.15 cc. and 0.2 cc. at weekly intervals intracutaneously. The

bleedings obtained before and those obtained after treatment of both groups were separately pooled and tested for protective value by mouse protection tests. The protection values of the "before" and "after" sera of Group 1 and the protective value of the "before" and "after" sera of Group 2 are shown in Table 2. In the protection tests 0.1 cc. of serum was injected intraperitoneally into mice, followed in ½ hour by varying concentrations of typhoid bacilli. A similar test was done upon each of 5 mice and the duration of survival noted. A pooled serum of 4 patients who previously had had typhoid fever was used as a control; in addition, the same number of organisms used as a test was injected into control mice without the addition of serum. Pooled sera were used in these experiments because of the fact that an enormous number of mice would have to be used if each individual serum was to be tested.

After a rough estimate of the protective dose was obtained by the above method, additional mice were treated with serum and culture in the manner indicated in Table 3, in order to obtain a somewhat clearer end point.

TABLE 1.

Agglutinating titer of group never previously immunized against typhoid 3 weeks after receiving *subcutaneously* at weekly intervals 0.5 cc., 1 cc. and 1 cc. of typhoid vaccine No. 97513 containing 2000 million *E. typhosus* per cc.

No.	Ant.	0.	20.	40.	80.	160.	320.	640.	1280.	2560.	Av.
45	"H"	0	0	0	1	1	11	15	12	5	921
45	"O"	10	6	9	11	3	3	1	2	0	155

Agglutinating titer of group never previously immunized against typhoid 3 weeks after receiving *intracutaneously* at weekly intervals 0.1 cc., 0.15 cc. and 0.2 cc. typhoid vaccine No. 97513 containing 2000 million *E. typhosus* per cc.

No.	Ant.	0.	20.	40.	80.	160.	320.	640.	1280.	2560.	Av.
56	"H"	0	0	0	2	3	12	17	11	11	1028
56	"O"	12	12	9	9	3	6	5	0	0	123

Results. *Antibody Studies.* These are indicated in the accompanying tables. As indicated in Table 1, the H agglutinin response of individuals treated with bacterin No. 97513 was quite satisfactory in both subcutaneously and intracutaneously treated groups, with a little better response possibly in the intracutaneously treated group, since 11 of the latter sera showed a titer of 2560, as contrasted with only 5 of the subcutaneously treated group. The O agglutinin response was much lower in both groups, being possibly somewhat less in the subcutaneously treated group. This low titer for O agglutinin is in accord with the experiences of others (except Perry) after typhoid vaccination.

It was hoped that by administering one dose of vaccine (0.1 cc. intracutaneously or 1 cc. subcutaneously) to sufficient number of individuals previously vaccinated, additional evidence would be obtained to substantiate the findings of Perry as to re-vaccination. Antibody determinations were obtained only on 4 individuals in each group. These showed rather high agglutination titers (640, 640, 1280 and 1280 in intracutaneous group; 320, 640, 1280 and 1280 in subcutaneous group). This, of course, suggests a good response but is too small a group to warrant definite conclusions.

Table 2 shows the results of the protection tests on the two groups receiving sensitized vaccine No. 26063. It is to be observed that the intracutaneously treated group showed up a little better than

TABLE 2.

Results of protection tests of pooled blood taken before and after treatment with sensitized typhoid vaccine No. 26063, 2000 million *E. typhosus* per cc.

Group.	Treatment status.	Test dose.		Survival (S) or hours after test mice died.					Protection against.
		Serum, cc.	M.l.d.						
1 Subcutaneous vaccine	Before	0.1	100	16	16	16	16	24	None
		0.1	1,000	16	16	16	16	16	
	After	0.1	100	S	S	S	S	S	100 m.l.d.'s
		0.1	1,000	16	16	16	16	S	
		0.1	10,000	16	16	16	16	16	
2 Intracutaneous vaccine	Before	0.1	100	16	24	24	40	S	None
		0.1	1,000	16	16	24	24	24	
	After	0.1	100	S	S	S	S	S	Between 100 and 1000 m.l.d.'s
		0.1	1,000	16	24	24	S	S	
		0.1	10,000	16	16	16	16	16	
Typhoid recovered		0.1	100	S	S	S	S	S	100 m.l.d.'s
		0.1	1,000	16	16	16	16	24	
		0.1	10,000	16	16	16	16	16	
	5000 *E. typhosus*			16	24	24	40	S	5000 *E. typhosus* = 1 m.l.d.
	50,000 *E. typhosus*			16	16	24	24	24	
	500,000 *E. typhosus*			16	16	16	16	16	
	5 million *E. typhosus*			16	16	16	16	16	

History of Culture used in Mouse Protection Tests.
E. typhosus Stock Culture No. 2447 (U. S. Army Panama Carrier Strain).
3 hours. Culture in Hygienic Laboratory Broth.
Culture diluted to 1000 million per cc. in 6% mucin.
Injection dose, 0.5 cc.

TABLE 3.—SUMMARY OF PROTECTION TESTS.

Group.	Treatment status.	Test doses.		Result.			Protection against.
		Serum. cc.	M.l.d.	Survival.	Death.	Survival. %.	
1 Subcutaneous vaccine	Before	0.1	100	0	10	0	None
		0.1	500	0	5	0	
		0.1	1,000	0	10	0	
	After	0.1	100	10	0	100	Sl. more than 100 m.l.d.'s
		0.1	500	1	4	20	
		0.1	1,000	1	9	10	
		0.1	10,000	0	5	0	
2 Intracutaneous vaccine	Before	0.1	100	2	8	20	Less than 100 m.l.d.'s
		0.1	500	0	5	0	
		0.1	1,000	0	10	0	
	After	0.1	100	10	0	100	More than 100 but less than 500 m.l.d.'s
		0.1	500	3	2	60	
		0.1	1,000	4	6	40	
		0.1	10,000	0	5	0	
Typhoid recovered		0.1	100	6	4	60	Slightly less than 100 m.l.d.'s
		0.1	500	0	5	0	
		0.1	1,000	0	10	0	
		0.1	10,000	0	5	0	

the subcutaneously treated group and seemed even slightly better than that of the recovered typhoid patients. When these sera were subjected to further study as indicated in Table 3, it is evident that the serum of the subcutaneously treated group had protective power against very slightly more than 100 m.l.d.'s of typhoid bacilli, whereas that of the intracutaneously treated group had protection against definitely more than 100 and slightly less than 500 m.l.d.'s. It is interesting to note that the protection in the latter group was greater than that of the convalescent typhoid sera.

Reactions. These as a whole were distinctly less marked in the intracutaneous group, a finding which is in accordance with our previous experience. The local reactions usually were quite mild and only in one instance was it sufficient to cause much discomfort. Except for slight nausea in one instance, mild vertigo in a second and slight general malaise in a third, no other constitutional symptoms were noted after a total of 168 doses had been given to the intracutaneous group. None of these individuals were in any way greatly incapacitated by these reactions.

The reactions, both local and general, in the subcutaneous group were much more marked. Headache, fever and malaise, lasting 48 hours, occurred in 5 instances; headache and malaise alone in 3 other instances and urticaria in 1. Most of these occurred after the second dose of 1 cc.

Comment. The results of these studies confirm our previous observations of the efficacy of intracutaneous typhoid vaccination, even though at present 3 doses (0.1, 0.15 and 0.2) were used in place of the original 4 doses. The agglutinin responses, both H and O, were just as good or even a trifle better after intracutaneous injection than after subcutaneous administration. The somatic or O agglutinins were also stimulated in both methods but not to as great an extent as the H type: this conforms to the experience of Dulaney and his co-workers[2] but is contrary to that of Perry[7] who found that these antibodies were stimulated to as great a degree as the H.

The results of the mouse-protection tests are quite interesting. They indicate that the protective power of the blood likewise is increased by typhoid vaccination and that here again, the intracutaneous method shows up better than the subcutaneous. It is to be admitted, since we had to use pooled sera in our experiment because of the expense entailed, that these tests can only be considered as rough guides or indicators of protective power; however, since this lack of sensitiveness applied equally to both groups, it still furnishes valuable evidence as to the efficacy of the intracutaneous method. It is interesting to note in passing that the protective power of the blood was better in both vaccinated groups than that of the blood of patients who previously had typhoid fever.

Although the number of cases was small, the fact that 8 previously vaccinated individuals showed such good antibody response after

the injection of a single dose of vaccine (0.1 cc. for intracutaneous and 1 cc. for subcutaneous group) helps to confirm similar findings by Perry and indicates that this method may be used to advantage in typhoid re-vaccination.

Finally, the marked difference in the degree of reactions in the two groups as well as the almost complete elimination of annoying constitutional symptoms in the intracutaneous group confirms the author's original observation of the advantages of the intracutaneous method of vaccination over the other routes of injection.

Conclusions. Further studies of intracutaneous typhoid vaccination confirmed the author's original observations as to the efficacy of this method, both from an immunologic standpoint as well as in the marked reduction of complete elimination of annoying reactions. In addition, evidence of satisfactory increase of the protective power of the blood and of stimulation of the somatic or O agglutinins was provided.

On the basis of these results, it is believed that the intracutaneous injection of 0.1 cc., 0.15 cc. and 0.2 cc. of the ordinary typhoid vaccine is the most satisfactory of any of the methods for typhoid immunization and should be more widely used. A single dose of 0.1 cc. seems adequate for immunization of previously vaccinated persons.

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THE NATURAL HISTORY AND DIAGNOSIS OF GASTRIC ULCER.*

By J. L. Drossner, M.D.,

SMITH, KLINE AND FRENCH FELLOW IN GASTRO-ENTEROLOGY,

AND

T. Grier Miller, M.D.,

PROFESSOR OF CLINICAL MEDICINE, PHILADELPHIA, PA.

(From the Gastro-Intestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic, Hospital of the University of Pennsylvania.)

Ulcer, carcinoma and chronic gastritis are the three organic diseases of the stomach that most often produce "indigestion." In

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our out-patient gastro-intestinal clinic each of these affections has accounted for approximately 4% of the cases with that syndrome; all together, for fewer than have been attributed to purely functional gastric disorders (17.5%). The truly common causes are extra-gastric, chiefly gall bladder disease, which has been responsible for 31%, and duodenal ulcer, responsible for 25%.

In spite of its comparative rarity clinically, in this country at least, gastric ulcer deserves and has received a great deal of attention because of the serious character of its complications and because of its similarity to that far more commonly recognized extra-gastric lesion, duodenal ulcer, with which it is confused and from which symptomatically it cannot be differentiated. The Quarterly Cumulative Index Medicus still groups the two diseases together, under the heading of peptic ulcer, and most authors, in their discussions of the etiology, diagnosis and treatment, do not clearly distinguish them. Although we must admit many similarities both pathologically and clinically, yet it is believed that some focusing of attention on gastric ulcer alone brings out certain important differences in the two diseases and clarifies thought about each of them.

Gastric ulcer, as a matter of fact, until comparatively recent years was not regarded as a particularly infrequent disease, and still is not so regarded in England. In Osler's System, C. F. Martin[4] 25 years ago stated that it was more common than duodenal ulcer in the ratio of 2 or 3 to 1. More recent roentgenologic study, however, has led us to believe the duodenal lesion to be 6 to 10 times as frequent. This change in our viewpoint is not due merely to the discovery that many of the ulcers formerly diagnosed as gastric were really duodenal, because the older statistics were based largely on objective findings at autopsy. Even modern necropsy reports support the claims of the older clinicians. Sturtevant and Shapiro,[7] in 1926, reviewing the records of 7700 autopsies at the Bellevue Hospital found almost 3 times as many healed and unhealed gastric as duodenal ulcers. Furthermore, Portis and Jaffe,[6] just a year ago, in a study of 9171 consecutive necropsies at the Cook County Hospital, found peptic ulcer in 457 cases about equally divided between the two organs. When the ulcer was an incidental finding, not related to the cause of death, they found that the gastric localization predominated; when it was acute, that it involved the stomach 4 times as often. Of the 118 essential ulcers, presumably diagnosed antemortem, the duodenum, however, was more often involved (63 to 55). Many of the acute lesions obviously heal without having produced symptoms, such as to lead to Roentgen examination, or our present roentgenologic methods fail to detect them. Furthermore, the symptoms and signs of many terminal and incidental gastric ulcers are presumably overlooked because of the predominance of other and more serious lesions. With the development of gastroscopy, however, we are beginning to appreciate the frequency

of superficial ulceration in connection with diffuse inflammatory lesions of the stomach. Thus, although duodenal ulcer is more easily and far more frequently recognized clinically, we must at the same time remember that the actual incidence of gastric ulcer is greater than our clinical data indicate, and that this is due, in part, to its occurrence in the acute form without symptoms and, in part, to its development in association with other and more serious intragastric and extra-gastric disease processes.

In order to get some first-hand information on the natural history and diagnosis of gastric ulcer we have reviewed the data on 111 cases observed in the medical clinic of our hospital during the last 10 years, and have included, for parts of the analysis to follow, data on 58 operatively proved cases, also from our hospital and reported in 1929 by Miller, Pendergrass and Andrews.[3] Thus the total series consists of 169 cases, all of which were diagnosed at operation or by the Roentgen ray. Naturally such a study does not include cases of the acute variety that give rise to no symptoms and heal spontaneously or the more chronic cases in which the presence of ulcer is masked by a more serious disease, but only such hospitalized and ambulant cases as we have been able to recognize clinically.

The sex and age incidences in the affected subjects deserve consideration because they differ from the accepted conception about them. Although the female sex has been said by some to be more commonly affected, 88% of our clinical group were in men (Tables 1 and 2). The age, furthermore, was more advanced than is generally believed, and was such as to eliminate this factor from consideration in the differentiation from gastric malignancy. At the time of examination, 67% were 40 or more years of age with the greatest incidence in the fifth decade (Table 1); this is slightly greater than for a comparable series of duodenal ulcer cases. Even if the age at the onset of the symptoms is considered this relationship still holds (Table 2). The women on the average were considerably older than the men.

TABLE 1.—AGE INCIDENCE, BY SEX, AT THE TIME OF ADMISSION TO HOSPITAL.

Decade.	Male.		Female.		Total group.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
10–19	1	0.7	..	..	1	0.6
20–29	17	12.1	3	10.4	20	11.8
30–39	33	23.6	2	6.9	35	20.8
40–49	39	27.9	6	20.6	45	26.6
50–59	28	20.0	8	27.6	36	21.3
60–69	17	12.1	8	27.6	25	14.8
70–79	5	3.6	2	6.9	7	4.1
Total	140	100.0	29	100.0	169	100.0

Recently, due largely to the influence of George Draper, we have become interested in the constitutional background of peptic ulcer, not only as an etiologic or diagnostic factor but also from the point

of view of its natural history. No one today questions that there is a physical, mental and emotional type of person who is predisposed to this disease. Draper's studies, however, were made on peptic ulcer subjects, gastric and duodenal, and probably largely duodenal, though he does not state the percentages. We suspect that if the two groups were separated not so many of the gastric ulcer patients would be found to be of the gracile, lantern-jawed, sensitive and nervously tense type, and yet such of our records as contained a statement as to body habitus indicate that 35% were of the so-called ulcer type, while only 12% were sthenic. We must admit, furthermore that many of them developed their ulcer when under great emotional strain: such strain may be effective only when the subject on some constitutional basis is predisposed. Constitutional equipment may also explain the hereditary tendency and the occurrence of ulcer in various members of a family. A family history indicative of ulcer was obtained in 14% of our patients.

TABLE 2.—AGE INCIDENCE, BY SEX, AT THE TIME OF ONSET OF SYMPTOMS.

Decade.	Male.		Female.		Total group.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
10–19 . . .	5	3.6	1	3.3	6	3.5
20–29 . . .	29	20.7	3	10.4	32	19.0
30–39 . . .	36	25.8	3	10.4	39	23.1
40–49 . . .	29	20.7	9	31.0	38	22.5
50–59 . . .	26	18.6	8	27.6	34	20.1
60–69 . . .	12	8.5	3	10.4	15	8.9
70–79 . . .	3	2.1	2	6.9	5	2.9
Total .	140	100.0	29	100.0	169	100.0

Average duration of symptoms on admission = 4 years.

A further item of evidence in favor of a constitutional factor for gastric ulcer in general is its frequent association with duodenal ulcer (17% in our group). Its association with other disease processes, such as those of the cardio-vascular, renal and nervous systems, and with carcinoma elsewhere in the body at least deserves mention and probably indicates the importance etiologically of impaired general bodily vigor. Duodenal stasis was demonstrated in 4% of our series and this also may be of etiologic significance.

Of the clinical cases of advanced gastric ulcer a surprising number heal under the influence, or perhaps it is fairer to say during the course, of a simple medical regimen. That such healing occurs is shown conclusively by the large scars previously referred to as having been observed at autopsy. Of our 111 cases, 79 were given a prolonged trial on a conservative medical program with at least temporary success in 63 (80%). Satisfactory follow-up roentgenologic investigation was accomplished in but 41 of these cases but it showed a complete disappearance of the niche within 1 to 3 months in 20 (49%), in 2 of which carcinoma had originally been suspected. Eleven others showed almost a complete disappearance;

7, a satisfactory decrease in size. In some instances the defect, even though at first quite large, could not be found after 2 to 3 weeks and no subsequent interruption in the passage of peristaltic waves could be detected. Some such cases have been followed for 5 to 7 years without a recurrence of subjective or objective evidence of activity. The fact that during the past 5 years we have subjected to surgery only one-half as many patients (25%) as during the preceding 5-year period indicates our increasing personal belief that clinical cure on a conservative basis is often attainable.

In spite of such encouraging results from medical management we still feel that, because of the possibility of malignancy, every case that fails to show an actual decrease in the size of the niche by Roentgen study within 2 to 3 weeks, no matter what the other conditions may be, deserves and demands prompt surgical exploration. Although we have, of course, excluded from the group under consideration those cases that proved to be malignant, some of the included number were denied a prolonged trial of medical therapy because of that possibility. Of 19 other cases, however, that were given a reasonable trial on a conservative basis and failed to improve, 4 had organic pyloric stenosis, 4 had gastric hyperacidity (not common in gastric ulcer), 13 were excessive users of alcohol or tobacco and 2 had duodenal stasis. We are inclined to believe that all of these are unfavorable factors for the healing of gastric ulcer.

Gastric ulcer, once healed, has a tendency to recur, as does duodenal ulcer, and this took place in 38% of 47 carefully followed cases. The precipitating factors seemed to be the same as those that produced the original lesion: indiscretions in diet, alcoholic excesses, nervous or emotional strain and infection. We have noted especially their recurrence after an upper respiratory infection. As to chronic focal infection we have observed no greater incidence in ulcer patients than in those with other diseases.

Sooner or later most of the gastric ulcers that do not heal develop complications: perforation, hemorrhage, stenosis or malignant degeneration (Table 3). Also, without actual perforation, the inflammatory reaction may extend beyond the stomach and involve such structures as the pancreas or intestine, giving rise to pancreatitis, adhesions, fistulæ and even intestinal obstruction.

TABLE 3.—INCIDENCE OF COMPLICATIONS IN TOTAL GROUP OF 169 CASES.

Complication.	Per cent.
Perforation	11
Hemorrhage	19
Stenosis (marked and organic)	4
Malignancy	0.9

Perforation occurred in 19% of our previously reported 58 cases, all of which, however, were eventually surgical; whereas the incidence was only 7% in our 111 cases studied primarily on a medical

service. The incidence for the total group was 11%. Only a few occurred without preceding ulcer symptoms, but in most instances such symptoms had been present less than a year. These ulcers were almost without exception on the anterior wall of the stomach.

Gross hemorrhage at one time or another in the life history of gastric ulcer is considered to occur in about 20%. Hurst[2] encountered it in 18%, which closely approximates the incidence in this series (19%). Hematemesis occurred in all but one of the bleeding cases.

Stenosis, when permanent, results from fibrosis and contraction about a pyloric or antral ulcer and consequently is encountered during or after healing, often after repeated periods of activity; when transient, it is explainable on the basis of an acute inflammatory reaction or of edema, as when the blood serum protein is reduced. Severe obstruction occurred in only 4% of our series. More often it results from duodenal ulcer, though the mistake of calling these stenosing duodenal lesions gastric is very common.

Ever since the statement of McCarty's original thesis that 68% of gastric ulcers are precancerous lesions, there has been a great deal of debate as to the actual frequency of this complication. Hurst estimated it was 6%. Recently Hinton and Trubek,[1] reviewing 104 cases, failed to find a single one with true malignant degeneration. In our series, only 1 case developed eventually malignancy in the border of an ulcer which had been present clinically for many years. Malignant degeneration undoubtedly occurs, but we have never seen any but the one ulcer that persisted for a long time, obviously as a benign lesion, take on malignant characteristics. We have seen many ulcerative gastric lesions, especially of the pylorus, that were clinically of uncertain nature and that proved to be malignant at operation. It is difficult to prove, however, that these were not malignant from the beginning. If ulcers of the pylorus frequently become malignant, one would expect that many of the cases subjected surgically merely to a gastro-enterostomy, because of the surgeon's belief that the lesion was benign, would ultimately develop cancer of the stomach. This, we believe, has only rarely occurred.

A clear conception of the diagnostic problems of gastric ulcer requires a familiarity with its natural history. If one knows the type of individual in which, and the circumstances under which, peptic ulcer commonly develops; if he appreciates the frequency of its occurrence without clear clinical manifestations, its tendency to persist together with a capacity to heal quickly and its liability to a recurrence of activity, and if he remembers the nature of its complications he is prepared to suspect its presence when any patient presents digestive symptoms that are not readily explainable on an obvious basis. Such a suspicion of the disease is the most important factor in the diagnosis and it should, in every instance,

lead to a roentgenologic investigation. Only by such a study can the diagnosis of peptic ulcer be made or eliminated with reasonable certainty; furthermore, such an examination usually establishes definitely whether it is gastric or duodenal and the exact localization within either organ. In Table 4 it will be seen that the Roentgen diagnosis in 80 proved cases of gastric ulcer was correct in 92%.

TABLE 4.—ROENTGENOLOGIC DIAGNOSIS IN 80 PROVED CASES OF GASTRIC ULCER.

Roentgen ray diagnosis.	No.	Operative or gastroscopic findings.
Ulcer of the lesser curvature	43	36 on lesser curvature; 3 on post. wall, 4 seen by gastroscope.
Ulcer of the greater curvature	3	1 on greater curv., 1 at pylorus, 1 proved gastroscopically.
Gastric ulcer, location not stated	4	1 each on lesser curv., greater curv. and post. wall. 1 not stated.
Ulcer probably on posterior wall	4	3 on post. wall (1 proved by gastroscope); 1 on lesser curv.
Pyloric ulcer	4	2 pyloric, 2 prepyloric.
Gastric ulcer or adhesions	5	1 hour-glass stomach, 1 lesser curv., 1 pyloric, 2 not stated.
Pyloric obstruction from ulcer	4	3 gastric ulcers with pyloric stenosis, 1 post. wall.
Marginal ulcer	2	2 lesser curvature.
Gastric ulcer or subtotal gastrectomy	2	2 lesser curvature.
Gastric ulcer or carcinoma	3	2 lesser curv., 1 large benign ulcer posterior wall.
Duodenal ulcer	1	1 lesser curvature.
Stomach negative	5	3 lesser curv. (1 perf.), 1 benign ulc. tumor, 1 seen gastroscopically.

Diagnosis correct in 92% of cases.

The history alone, when it includes epigastric discomfort in a fixed relationship to food and relief by food and especially when it covers a period of years with prolonged asymptomatic intervals, may indicate the diagnosis, but this today should never be accepted as a substitute for Roentgen identification. The physical examination, important as it is to eliminate other lesions, rarely aids greatly in the exact diagnosis of an uncomplicated case. Determination of the acidity of the gastric contents, helpful in duodenal ulcer, cannot be considered of much value in gastric ulcer. The incidence of hyperchlorhydria (Fig. 1) is only slightly higher than that frequently found in normal individuals. Achlorhydria occurred in 6% of our cases, even after histamine. Interestingly the achlorhydria cases were on the average 10 years older than the rest of our group. Most of them were at first suspected of having a malignant ulcer, but none, so far as we know, has developed convincing signs, though half of them have been carefully followed for more than a year. All responded satisfactorily to a medical regimen.

Gastroscopy deserves consideration as a diagnostic procedure. It was employed in but 12 of our cases but by means of it the diagnosis was established in 9. Certainly in those cases in which the diagnosis is suspected but the Roentgen examination is negative

or questionable its aid should be invoked. Schindler[5] claims that in a series of 50 cases the diagnosis was made gastroscopically in 6 that had a negative Roentgen study.

With the natural history of gastric ulcer in mind, the diagnosis of the complications should present little difficulty. Perforation and hemorrhage are dramatic events but, in our experience, only rarely occur as the initial manifestation of ulcer. Even when perforation does so occur, the character of the attack, the physical

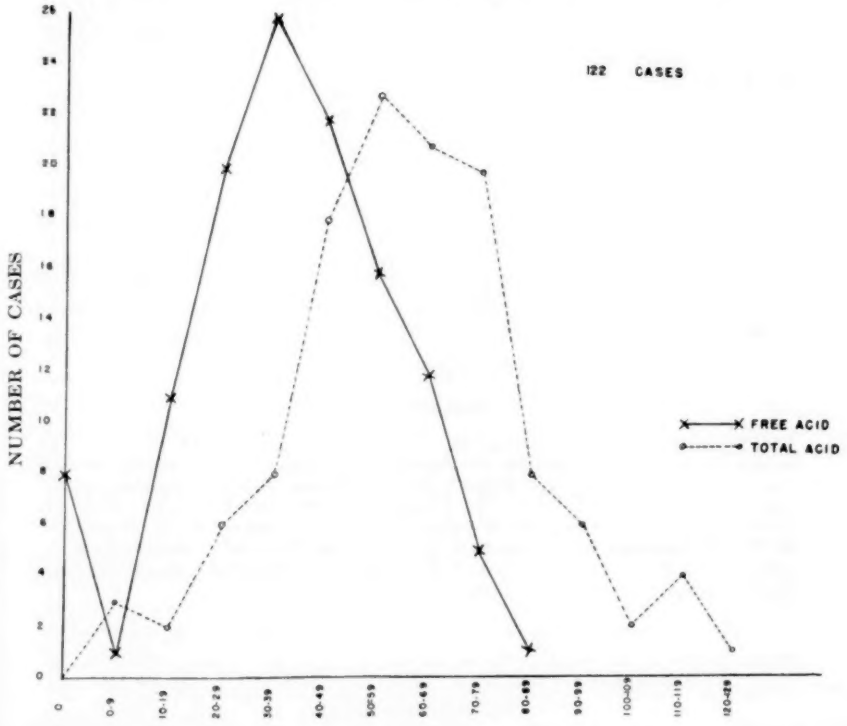

FIG. 1.—The maximal free hydrochloric acid and total acidity of the gastric contents in 122 of the cases of gastric ulcer.

signs and the demonstration, by the Roentgen ray, of air under the diaphragm is sufficient to establish the diagnosis. Since two-thirds of all massive hemorrhage from the stomach is due to peptic ulcer and most of the others to splenic anemia or cirrhosis of the liver, usually easily recognized conditions, we are rarely in doubt as to the cause of such bleeding. Stenosis, though easily recognized by gastric analysis or the Roentgen study is not always of a permanent nature and its pathology, whether acutely inflammatory,

cicatricial or purely edematous as a result of serum protein loss from the blood, deserves special diagnostic study. Malignancy, as stated before, must always be considered and can usually be diagnosed on the basis of the response to medical therapy as determined by repeated roentgenologic investigations.

Summary. The natural history and diagnosis of gastric ulcer have been considered in connection with an analysis of certain data from the records of 169 personally observed cases. The results suggest:

1. That gastric ulcer deserves attention apart from duodenal ulcer;
2. That it often is unrecognized clinically: sometimes because it presents no symptoms, sometimes because the symptoms are masked by those of other more serious disease processes;
3. That healing tends to occur naturally and, even in the recognized and treated cases, usually occurs on a simple medical regimen;
4. That, however, a recurrence of activity is common (38% of our carefully observed cases) and may be precipitated by such factors as gastric hyperacidity, dietary indiscretion, the excessive use of alcohol, emotional upset, or infection;
5. That the diagnosis of gastric ulcer and of its complications will be most readily made by those who have knowledge of its natural history and who subject promptly all questionable cases to roentgenologic and gastroscopic investigation.

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EVIDENCE REGARDING THE CONTROL OF HEPATIC GLYCOGENOLYSIS.

By W. B. Cannon,

GEORGE HIGGINSON PROFESSOR OF PHYSIOLOGY, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

(From the Department of Physiology in the Harvard Medical School.)

Are there glycosecretory nerves distributed to the liver cells? Older investigators found that section of the splanchnic nerves prevented the "puncture diabetes" of Claude Bernard, and they drew the conclusion that these were the secretory nerves. In 1894, Cavazzani[10] thought he had brought proof for this view by finding less glycogen in the liver, when it was stimulated from the celiac plexus after death, than was present before the stimulation began. Wertheimer and Battez[23] pointed out, however, that the result

could be explained by *postmortem* glycogenolysis. Meanwhile, Kaufmann[13] had shown that cutting the hepatic nerves did not prevent *piqûre* from having its usual hyperglycemic effect. In 1901, Blum[1] reported his important observation that subcutaneous injections of adrenaline produced hyperglycemia and glycosuria. Thereupon Mayer[17] raised the question whether Bernard's *piqûre* might not induce glycosuria by causing a discharge of adrenaline from the adrenal medulla. After producing *piqûre* glycosuria in all 6 rabbits tested, he removed the adrenals from 25 rabbits, and found that *piqûre* did not cause glycosuria in any of them. Three years later Gautrelet and Thomas[11] reported that splanchnic stimulation in adrenalectomized dogs did not provoke a glycosuria. In 1912, Macleod and Pearce[16] confirmed these observations by showing that when in dogs the adrenal gland is removed on one side splanchnic stimulation on that side is not followed by the usual hyperglycogenolysis. They found, however, that when they excited the hepatic plexus they elicited a marked hyperglycemia, but only if the adrenal glands were intact. The opinion was ventured that "some influence exercised by the adrenal glands is evidently essential for the functional integrity of the nerves which control the process of glycogenolysis." These observations still left a function for the nerves to perform in liberating glucose from the hepatic stores.

In a study of reflex hyperglycemia Griffith[12] to some degree supported earlier conclusions, but he also raised puzzling questions. Stimulation of afferent nerves produced a prompt increase of blood sugar. This effect was not decreased by cutting hepatic nerves; on the average it was reduced, however, but not abolished, if the adrenals were excluded from action. And in animals with hepatic nerves severed and adrenals excluded, afferent nerve stimulation still had as great an effect as when the adrenals alone were out of function. Here is evidence that the nervous influences on the liver are effective, though of minor importance, but the problem is presented of accounting for glycogenolysis when both nervous and humoral (medulliadrenal) agencies are inoperative.

Further testimony regarding control of liver glycogen was offered by Bulatao and Cannon[5] in observations on cats exhibiting "sham rage." The signs of rage in these decorticated animals, out of anesthesia, was attended by a gradually increasing hyperglycemia which might rise to 500 mg.·%. If the hepatic nerves were severed, without disturbing the adrenal glands, there was still a rise in the glycemic level during the period of pseudaffective activity. On the other hand, when the possibility of adrenal participation was excluded, the initial hyperglycemia (due to operative procedures) declined during the period.

The observations of Britton[3] on emotional hyperglycemia were quite in harmony with those on "sham rage." Increases of blood sugar, ranging from 30 to 90% in normal unanesthetized animals,

were noted after 2 minutes of excitement. When the liver nerves had been cut, and the adrenals left innervated, the effects of excitement were only slightly modified. Conversely, when functioning of the adrenal medulla had been excluded, emotional states, quite as intense as in normal animals, were usually accompanied, not by an increase, but by a decrease, of the blood-sugar concentration. The decrease might persist for 20 minutes or longer.

The foregoing evidence, favorable in some instances to direct nervous control of hepatic glycogenolysis and in other instances to hormonal control alone, through medulliadrenal secretion, is matched by discordant testimony of histologists. Riegele[21] has described a network of extremely delicate nerve filaments between the liver cells, with offshoots reaching into the cellular cytoplasm. This observation, if correct, would establish a basis for immediate nervous government of liver function. The existence of a nervous "terminal reticulum," however, has been questioned by Nonidez,[20] who reports that the silver method used by Riegele to stain nerve fibers may also impregnate fine connective tissue strands and thus confuse the picture. "Up to the present," Nonidez declares, "no nervous structure resembling a network has been described in the liver." This testimony would leave the management of liver functions to physical and chemical agencies operating in the blood supply.

Recent experiments, performed by Cannon and Lissák,[8] have brought support to the inference that glycogenolysis is not controlled by direct action of nerve impulses on liver cells. These investigators demonstrated a substance, in all respects like adrenaline in its effects, which can be extracted from the ultimate sympathetic neurones, whether these neurones, or parts of them, are isolated or are embedded in organs (*e. g.*, the heart). The significant fact appears that whereas extracts of liver blood-vessels raise blood pressure, dilate the pupil and augment cardiac contraction, extracts of liver pulp have little or no adrenaline-like action. In consideration of the difficulty of removing the pulp from the vessels without pulling away vascular twigs, the occasional slight action of the pulp is explicable without need of assuming presence of sympathetic endings on the hepatic cells. In view of the enormous numbers of these cells and the small size of the nerves which accompany the hepatic artery, it is obvious that the fibers in these nerves would have to branch to an almost incredible degree in order to reach to even a majority of the cellular units in the liver. Furthermore, there is no evidence that such branching occurs. Indeed, histologic studies, as Nonidez has remarked, provide no indication of an innervation of the hepatic cells.

If the hepatic cells are not subject to sympathetic impulses, but are subject to secreted adrenaline, there would be explained the efficacy of *piqûre* after severance of the hepatic nerves (Kaufmann), the failure of *piqûre* to produce glycosuria in the absence of the

adrenals (Mayer), and the absence of glycosuria when the splanchnics are stimulated in adrenalectomized animals (Gautrelet and Thomas, Macleod and Pearce). There would also be explained the absence of hyperglycemia in "sham rage" (Bulatao and Cannon) and in emotional states (Britton) when the adrenal medulla is nonfunctional, although nerves to the liver are intact, and the marked hyperglycemia in these states when the hepatic nerves are cut and the adrenals are left innervated.

The observations of Macleod and Pearce and also of Griffith call for discussion. The former two investigators reported a notable hyperglycemia when they excited the hepatic plexus, but only when the adrenal glands were intact. It is pertinent to note that under experimental conditions there is a discharge of adrenaline from the adrenals (Cannon and Rapport[9]) and consequently the anesthesia and the laparotomy incidental to stimulating the nerves on the hepatic artery would have the result which Macleod and Pearce noted. If the adrenal glands were rendered inactive the same operation would be ineffective.

For an explanation of the hyperglycemia recorded by Griffith, occurring when an afferent nerve was excited even though the hepatic nerves were cut and the adrenal medulla was out of action, the experiments of Bodo and Benaglia[2] are significant. In 1922, Cannon and Griffith[7] studied the characteristics of a substance, given off from the liver when its nerves were stimulated, that was like adrenaline in causing a rise of blood pressure and an acceleration of the heart. Later (Cannon and Bacq[6]) such a substance was shown to be liberated into the blood stream wherever sympathetic nerves were activated and was given the name "sympathin." Under ether anesthesia its presence was difficult to demonstrate, but under chloralose it readily manifested its properties. Bodo and Benaglia, using chloralose as an anesthetic, found that sympathin produced by exciting the cardio-accelerator nerves caused hyperglycemia in animals with liver nerves and adrenals both excluded from action. And in such animals, also, they observed that emotional excitement, known to produce sympathin (Newton, Zwemer and Cannon[18]), induced a rise of blood sugar. Griffith employed chloralose in his experiments, and since there can be a reflex production of sympathin (Liu and Rosenblueth[14]), quite possibly the reflex hyperglycemia observed by him in animals with denervated liver and adrenals was due to the action of sympathin. It is noteworthy that some of the sympathin might act on coming to the liver from elsewhere, as from the heart, and some might be produced locally in the hepatic vessels and have a local effect.

In the foregoing paragraphs the main features in the evidence regarding control of hepatic glycogenolysis have been reviewed. It has been shown that the facts at hand indicate that the liver cells are not directly subject to sympathetic control, but respond to

adrenaline from the adrenal medulla, and also to circulating sympathin, by a liberation of glucose. The only anomalous feature in this situation is the existence of a highly important organ in the body, the liver, which adrenaline readily affects, though not acting then as a sympathicomimetic agent. Pertinent to this curious anomaly is the action of ergotamine in preventing the hyperglycemia which results from cerebral lesions and from adrenaline (Nitzescu and Munteanu;[19] Long[15]). Ergotamine, as is well known, blocks the positive action of both sympathetic impulses and adrenaline in structures demonstrably innervated by sympathetic fibers.

The foregoing evidence is related to nervous management of glycogenolysis. It appears that the liver can operate satisfactorily, quite independently of that management, both to take in and give forth glucose. Soskin, Essex, Herrick and Mann[22] have shown, by determining simultaneously the rate of blood flow through the liver and the glucose content of the inflowing and outflowing blood, that during control periods the liver secretes glucose, but when glucose is abundantly supplied, secretion ceases and sugar is retained. And consistent with this observation, Brouha, Cannon and Dill[4] have recently noted that after complete removal of the sympathetic system the glycemic level is kept normal, even in vigorous exercise.

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A SIMPLIFIED METHOD FOR CALCULATING DIABETIC DIETS.

By Russell Richardson, M.D.,

CHIEF, METABOLIC SECTION OF THE MEDICAL CLINIC, HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA; ASSISTANT PROFESSOR OF MEDICINE, AND ASSOCIATE, GEORGE S. COX MEDICAL RESEARCH INSTITUTE, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

In order to calculate a diabetic diet it is necessary to know the average serving in grams of the desired food, the percentage of protein, fat, and carbohydrate in each food and the customary distri-

bution of foods among the meals. This information is ordinarily readily available only to the trained dietitian.

The following plan for calculating diets is offered as a simple method which can be used with a minimum expenditure of time. Furthermore, it requires no unusual training in diet work nor further knowledge regarding foods than is possessed by most physicians. Herewith is shown the protein, fat and carbohydrate content of seven diets, increasing in each diet by 5 gm. protein, 10 gm. fat, and 25 gm. carbohydrate.* On the following pages is shown a distribution of foods corresponding to these figures arranged in the form of diets. It will be noted that bread and butter are included in all diets. Diet No. 1 is suggested as a "starvation diet" for short-time use in order to lower the blood sugar rapidly.

TABLE 1.—SEVEN DIETARY COMBINATIONS WITH CALORIC VALUES.

	Protein.	*Fat.*	*Carb.*	*Calories.*
No. 1	50	25	25	525
No. 2	50	50	50	850
No. 3	55	60	75	1060
No. 4	60	70	100	1270
No. 5	65	80	125	1480
No. 6	70	90	150	1690
No. 7	75	100	175	1900

DIET NO. 1.—(P/50, F/25, C/25—CALORIES, 525).

	Protein.	*Fat.*	*Carbohydrate.*
Breakfast:			
½ small grapefruit	1	..	5
or ½ medium orange	(1)	..	(5)
or 1½ tblsp. oatmeal (cooked)	(1)	..	(6)
1 egg plus 1 egg white	12	6	..
2 tblsp. cream	1	6	1
or ½ square butter	..	(5)	..
Lunch:			
1 bowl clear meat broth*			
1 egg white	6	..	..
½ head lettuce with small amount lemon juice or vinegar	1	..	2
4 tblsp. cottage cheese	15	..	1
½ slice bread	1	..	5
½ square butter	..	5	..
Supper:			
1 bowl clear meat broth*			
3 tblsp. 5% vegetable	1	..	3
3 tblsp. 10% vegetable	2	..	6
2 oz. lean meat, fish or chicken	12	10	..
½ slice bread	1	..	5
	53	27	28

Coffee or tea.
* If desired.

* Taken from Bull. No. 28, U. S. Dept. of Agriculture, and from "Tables of Food Values" by Alice V. Bradley.

DIET No. 2.—(P/50, F/50, C/50—CALORIES, 850).

	Protein.	*Fat.*	*Carbohydrate.*
Breakfast:			
½ cup grapefruit	1	..	10
3 tblsp. oatmeal (cooked)	3	..	12
1 egg	6	6	..
1 square butter	..	10	..
or 4 tblsp. cream	(2)	(12)	(2)
½ slice bread	1	..	5
Lunch:			
1 bowl clear meat broth*			
4–5 small strips bacon	3	9	..
½ head lettuce	1	..	2
2 tblsp. cottage cheese	8	..	..
3 tblsp. 5% vegetable	1	..	3
½ slice bread	1	..	5
½ square butter	..	5	
Supper:			
1 bowl clear meat broth*			
3 tblsp. 5% vegetable	1	..	3
3 tblsp. 10% vegetable	2	..	6
3 oz. lean meat, fish or chicken	18	15	..
½ slice bread	1	..	5
½ square butter	..	5	..
	47	50	51

Coffee or tea.
* If desired.

DIET No. 3.—(P/55, F/60, C/75—CALORIES, 1060).

	Protein.	*Fat.*	*Carbohydrate.*
Breakfast:			
½ cup grapefruit	1	..	10
1 medium sized orange	..	..	(10)
3 tblsp. oatmeal (cooked)	3	..	12
1 egg	6	6	..
2 tblsp. cream	1	6	..
½ slice bread	1	..	7½
½ square butter	..	5	..
Lunch:			
1 egg	6	6	..
4–5 strips bacon	3	9	..
3 tblsp. 5% vegetable	1	..	3
3 tblsp. 10% vegetable	2	..	6
1 slice bread	2	..	15
½ square butter	..	5	..
Supper:			
1 bowl clear meat broth*			
3 tblsp. 5% vegetable	1	..	3
3 tblsp. 10% vegetable	2	..	6
¼ pound lean meat, fish, or chicken	24	20	..
1 slice bread	2	..	15
½ square butter	..	5	..
	55	62	78

Coffee or tea.
* If desired.

DIET NO. 4.—(P/60, F/70, C/100—CALORIES, 1270).

	Protein.	*Fat.*	*Carbohydrate.*
Breakfast:			
½ cup grapefruit	1	..	10
1 medium sized orange	..	..	(10)
3 tblsp. oatmeal (cooked)	3	..	12
1 egg	6	6	..
4 tblsp. cream	2	12	2
1 slice bread	2	..	15
½ square butter	..	5	..
Lunch:			
1 egg and 1 egg white	12	6	..
½ head lettuce	1	..	2
2 level tsp. mayonnaise	..	10	..
3 tblsp. 5% vegetable	1	..	3
3 tblsp. 10% vegetable	2	..	6
1 slice bread	2	..	15
½ square butter	..	5	..
Supper:			
1 bowl clear meat broth*			
3 tblsp. 5% vegetable	1	..	3
3 tblsp. 10% vegetable	2	..	6
¼ pound lean meat, fish or chicken	24	20	..
1 slice bread	2	..	15
½ square butter	..	5	..
1 medium sized orange	1	..	10
	62	69	99

Coffee or tea.
* If desired.

DIET NO. 5.—(P/65, F/80, C/125—CALORIES, 1480).

	Protein.	*Fat.*	*Carbohydrate.*
Breakfast:			
½ cup grapefruit	1	..	10
1 medium-sized orange	..	..	(10)
5 tblsp. oatmeal (cooked)	5	..	20
1 egg	6	6	..
4 tblsp. cream	2	12	2
1 slice bread	2	..	15
½ square butter	..	5	..
Lunch:			
1 egg and 1 egg white	12	6	
3 tblsp. 5% vegetable	1	..	3
3 tblsp. 10% vegetable	2	..	6
½ head lettuce	1	..	2
2 level tsp. mayonnaise	..	10	..
2 slices bread	4	..	30
1 square butter	..	10	
Supper:			
1 bowl clear meat broth*			
3 tblsp. 5% vegetable	1	..	3
3 tblsp. 10% vegetable	2	..	6
¼ pound lean meat, fish or chicken	24	20	..
2 slices bread	4	..	30
1 square butter	..	10	..
1 medium sized orange	..	..	10
	67	79	137

Coffee or tea.
* If desired.

DIET NO. 6.—(P/70, F/90, C/150—CALORIES, 1690).

	Protein.	*Fat.*	*Carbohydrate.*
Breakfast:			
½ cup grapefruit	1	..	10
1 medium sized orange	..	..	(10)
5 tblsp. oatmeal (cooked)	5	..	20
2 eggs	12	12	..
4 tblsp. cream	2	12	2
2 slices bread	4	..	30
1 square butter	..	10	..
Lunch:			
1 egg	6	6	..
3 tblsp. 5% vegetable	1	..	3
3 tblsp. 10% vegetable	2	..	6
½ head lettuce	1	..	2
1 level tsp. mayonnaise	..	5	..
2 slices bread	4	..	30
1 square butter	..	10	
Supper:			
1 bowl meat broth*			
3 tblsp. 5% vegetable	1	..	3
3 tblsp. 10% vegetable	2	..	6
¼ pound lean meat, fish, or chicken	24	20	..
2 slices bread	4	..	30
1 square butter	..	10	..
2 tblsp. cream	1	6	1
1 medium sized orange	..	..	10
	70	91	153

Coffee or tea.
* If desired.

DIET NO. 7.—(P/75, F/100, C/175—CALORIES, 1900).

	Protein.	*Fat.*	*Carbohydrate.*
Breakfast:			
½ cup grapefruit	1	..	10
1 medium sized orange	..	..	(10)
5 tblsp. oatmeal (cooked)	5	..	20
2 eggs	12	12	..
4 tblsp. cream	2	12	2
2 slices bread	4	..	30
1 square butter	..	10	..
Lunch:			
1 egg and 1 egg white	12	6	
3 tblsp. 5% vegetable	1	..	3
3 tblsp. 10% vegetable	2	..	6
½ head lettuce	1	..	2
2 level tsp. mayonnaise	..	10	..
2 slices bread	4	..	30
1½ squares butter	..	15	
Supper:			
1 bowl clear meat broth*			
3 tblsp. 5% vegetable	1	..	3
3 tblsp. 10% vegetable	2	..	6
¼ pound lean meat, fish, or chicken	24	20	..
1 medium potato	2	..	20
2 slices bread	4	..	30
1½ squares butter	..	15	..
1 medium sized orange	..	..	10
	77	100	172

Coffee or tea.
* If desired.

In order to use the diets, find in Table 1 the diet that gives the amount of protein desired. On turning to the diet with this percentage of protein, it is evident that only bread and butter need be altered in order to arrive at the desired amount and arrangement of fat and carbohydrate. As a standard slice of bread as cut by machine contains 15 gm. of carbohydrate, and as a ½ inch thick slice of butter from the standard quarter-pound bar contains 10 gm. of fat, the diet given can be readily altered by the addition or subtraction of either or both of these foods.

TABLE 2.—FOOD VALUES.

	Protein	*Fat*	*Carbohydrate*
1 slice bread	2	..	15
1 Uneeda biscuit	1	..	5
1 graham cracker	1	1	8
1 medium-sized potato	2	..	20
3 tblsp. oatmeal (cooked)	3	..	12
1 medium-sized egg	6	6	..
¼ lb. lean meat, fish or chicken	24	20	..
2 oz. cottage cheese (60 gm.)	13	1	..
1 square butter	..	10	..
1 tsp. mayonnaise	..	5	..
3 strips bacon	2	8	0
2 tblsp. 20% table cream	1	6	1
1 glass milk (½ pint)	8	10	12
1 glass buttermilk	8	1	12
1 tblsp. peanut butter	5	8	3
1 tblsp. cocoa	1	2	2
3 tblsp. 5% vegetable	1	..	3
3 tblsp. 10% vegetable	2	..	6

The following fresh fruits in the amounts given may be used with a food value of P/1, F/0, C/10:

½ cup grapefruit
1 medium sized orange
1½ medium sized peaches
1 slice pineapple, ½-inch thick
1 cup strawberries
1 slice watermelon, 6 inches by ¾ inch
½ of 4¼-inch cantaloupe
½ large apple
½ banana

Water, clear broths (broths and consommé without food value, such as commercial canned broths), coffee, tea, cocoa shells, and cracked cocoa can be taken without allowance for food content.

One slice bread equals one slice from standard sliced loaf.

One square butter equals one square ½ inch thick from ¼ pound bar.

Tblsp. equals one tablespoon.

Tsp. equals one teaspoon.

TABLE 3.—SUBSTITUTES.

Substitutes for 3 tablespoons cooked oatmeal:

½ cup corn flakes	1 cup puffed rice
½ cup Cream of Wheat (cooked)	1 cup puffed wheat
½ cup farina (cooked)	½ shredded wheat biscuit
2 tablespoons Grapenuts	3 tablespoons Wheatena (cooked)

Substitutes for 1 square of butter:

2 squares American pale cheese	2½ squares Full Cream cheese
2 squares Cheddar cheese	2½ squares Edam cheese
2½ squares Roquefort cheese	2 squares Swiss cheese
2½ squares Limburger cheese	3 squares Camembert cheese

Substitutes for 1 slice of bread:

1½ baking powder biscuit, 2 inches in diameter
¾ slice Boston Brown bread, 3 by ¾ inch in diameter
1½ bran muffin, 2 inches in diameter
1 egg muffin, 2 inches in diameter
½ slice raisin bread, 4 by 4 by ¾ inch.
1 Parkerhouse roll (large)
½ slice cinnamon toast, 4 by 4 by ⅛ inch
3 pieces Melba toast, 4 by 4 by ⅛ inch
6 saltines
3 soda crackers
2 graham crackers
1 cup pop corn

2 tsp. honey	3 tsp. jam
2 tsp. maple syrup	3 tsp. marmalade
2 tsp. molasses	

TABLE 4.—VEGETABLES.

5% *Vegetables.*		10% *Vegetables.*
Artichokes	Lettuce	Beets
Asparagus	Rhubarb	Carrots
String beans	Sauerkraut	Onions
Brussells sprouts	Tomato	Green peas (canned)
Cabbage	Spinach	Pumpkin
Celery	Swiss Chard	Squash
Cucumber	Dandelion greens	Turnips
Endive	Beet greens	Mushrooms
Egg plant	Water Cress	

15% *Vegetables.*	20% *Vegetables.*
Parsnips	Potatoes
Lima beans	Shell beans
Green peas (fresh)	Boiled rice
	Boiled macaroni

In addition to the variation in the diets by the use of different meats and vegetables, further variation can be obtained by the substitution of some of the common foods listed in Table 2. Other substitutes which may be used for oatmeal, bread and butter are shown in Table 3. If a larger diet than No. 7 (P/75, F/100 C/175) is desired, bread may be added as needed. It will seldom be necessary to add protein or fat to this diet.

When these diets are used with protamine zinc insulin, a meal should be added at about 10.30 P.M., consisting of ½ glass milk, 3 saltines and 1 level teaspoonful of peanut butter (P/6, F/8, C/14—150 calories.)

BOOK REVIEWS AND NOTICES

A Handbook of Elementary Psychobiology and Psychiatry. By Edward G. Billings, B.S., M.D., M.D. Cum Laude (Ind.), Assistant Professor of Psychiatry, University of Colorado School of Medicine; Director, the Psychiatric Liaison Department of the Colorado General and Psychopathic Hospitals; etc. Pp. 271; 10 figures. New York: The Macmillan Company, 1939. Price, $2.00.

In full accord with the teachings of Adolph Meyer, the contents are discussed under the headings of Psychobiology, Psychiatric Examination Procedures, General Psychopathology, General Principles of Psychotherapy and Selected References to Other Works Dealing with Personality Functioning and Psychiatry.

"Psychobiology is the science having to do with the study and understanding of the mentally integrated human organism." Another of the several definitions gives it as "the science and understanding of the study of both overt and implicit activity into a 'mentally integrated behavior'—normal and abnormal." Half of the volume is given to general consideration of psychopathology. Among other subjects discussed are normal and abnormal personality functioning; intellectual inadequacy reactions and constitutional psychopathic reactions; minor and major psychoses; disorientative-hallucinatory states; disorders of personality resulting from structural involvements of the brain; and psychopathologic problems of childhood. Hysterical disorders are referred to as "dissociative-dysmensic-substitution" phenomena, and are *conversion* substitutes for repressed thoughts disturbing life experiences to which there is aversion.

While psychobiologists do not show the avidity of psychoanalysts for coining words, frequent employment of Greek derivatives, "ergasiastics" or "ergasiarty," meaning psychiatry, "holergasia," "hypothymergasia," and many more corresponding terms, may seem a bit pedantic to medical groups without psychiatric training for whom this handbook is intended. The work admirably supplements our numerous psychiatric textbooks already in use. There is an exceptionally informative index.

N. Y.

A Textbook of Bacteriology. The Application of Bacteriology and Immunology to the Etiology, Diagnosis, Specific Therapy and Prevention of Infectious Diseases for Students and Practitioners of Medicine and Public Health. By Hans Zinsser, M.D., Consulting Bacteriologist to the Peter Bent Brigham and the Children's Hospitals, Boston, and Stanhope Bayne-Jones, M.D., Professor of Bacteriology and Dean, Yale University Medical School; Master of Trumbull College, Yale University, New Haven. Pp. 990; 116 illustrations. Eighth Edition, revised and reset. New York: D. Appleton-Century Company, Inc., 1939. Price, $8.00.

Though five years have elapsed since the appearance of the 7th edition, two additional copyrights in the interim show how actively this book has been sought by readers and kept up to date by the authors, in spite of the necessary increases in size and complexity. The section on pathogenic protozoa has been omitted for this edition, perhaps partly on this account, and a slight reduction in size has been obtained. The changes required by

the rapid advances in bacteriology and immunology are too numerous to mention here. They combine in maintaining this work as one of the best in its field.

THE MEDICAL CLINICS OF NORTH AMERICA, Vol. 23, No. 4 (Mayo Clinic Number, July, 1939). Pp. 284; 7 illus rations. Philadelphia: W. B. Saunders Company, 1939.

THIS Mayo Clinic number includes a symposium on dyspepsia, and 14 articles on miscellaneous subjects. The use of sulphanilamide, and the treatment of diabetes, syphilis, pneumonia and hypertension occupy prominent positions.

LES INFECTIONS HUMAINES À B. BIPOLARIS SEPTICUS (PASTEURELLOSES). By ROBERT REGAMEY, Assistant à l'Institut d'Hygiène et de Bactériologie de l'Université de Berne et Chef du laboratorie de recherches expérimentales à l'Institut sérothérapique et vaccinal Suisse à Berne. Pp. 126; 3 illustrations. Berne: Hans Huber, 1939.

THE first part is devoted to a short description of *B. bipolaris septicus*. Part II describes experimental pasteurellosis in the rabbit, mouse and guinea pig. Part III is a critical study of pasteurellosis in humans described in the literature, and the last part is a few pages devoted to an analysis of the origin of pasteurellosis in humans. H. M.

CLINICAL DIAGNOSIS BY LABORATORY METHODS. A Working Manual of Clinical Pathology. By JAMES CAMPBELL TODD, PH.B., M.D., Late Professor of Clinical Pathology, University of Colorado, School of Medicine, and ARTHUR HAWLEY SANFORD, A.M., M.D., Professor of Clinical Pathology, University of Minnesota (The Mayo Foundation); Head of Division on Clinical Laboratories, Mayo Clinic. Pp. 841; 368 illustrations (29 in colors). Ninth edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1939. Price, $6.00.

THIS excellent manual, of which a new edition has appeared every 3 or 4 years, continues to offer a wealth of well-considered, accurate information for workers in the clinical laboratory.

JOHN HOWARD (1726–1790). HOSPITAL AND PRISON REFORMER: A BIBLIOGRAPHY. By LEONA BAUMGARTNER, M.D., PH.D., with Introduction by ARNOLD M. MUIRHEAD, M.A. (OXON.). Pp. 79; 9 illustrations. Baltimore: The Johns Hopkins Press, 1939. Price, $1.00.

THE philanthropist John Howard should be revered for his years of struggle for the improvement of public health as well as for prison reform. Modestly calling himself a plodder who collected material for men of genius to use, he spent his last 17 years searching through England, Wales and all the countries of Europe for data on the appalling conditions of prisons and hospitals, until his death of "camp fever" in Russia in 1790 while inspecting military hospitals. The present bibliography of 204 items, reprinted from the *Bulletin of Medical History*, is a scholarly production enlivened by frequent notes and a listing of the present location of known copies of his writings, and especially by the appreciative biographic introduction by A. M. Muirhead. E. K.

SYMPOSIUM ON THE SYNAPSE. By HERBERT S. GASSER, JOSEPH ERLANGER, DETLEV W. BRONK, RAFAEL LORENTE DE NÓ, ALEXANDER FORBES. (Reprinted from *Journal of Neurophysiology*, **2**, 361–472, 1939). Pp. 113; illustrated. Springfield, Ill.: Charles C Thomas, 1939. Price, Bound, $2.00; Paper cover, $1.50.

THOSE interested in neurophysiology are deeply indebted for the publication of this series of brilliant discussions of a subject of controversy so protracted and so important. The leaders in the field are here, each at his best or near it, and each writing in a manner so characteristic as to render the work as fascinating to the biographer as to the experimenter. Only one serious stricture can be laid upon it, or rather upon those responsible for the symposium—that it is not sufficiently inclusive. In a controversy we like to see both sides equally represented. Of the 5 authors, 3 argue for an electrical mechanism, 1 for a chemical, and 1 for a dualistic hypothesis. Could we have had under the same cover a discussion by Dr. Cannon or Dr. Rosenblueth, for instance, the book would have been more fairly representative of current opinion. Yet we have a feast as it is and of the best. No less churlish reviewer would grumble for more.

We cannot close without a word of gratitude for the most appropriate dedication to Sir Charles Sherrington. G. McC.

DISEASES OF THE SKIN. By RICHARD L. SUTTON, M.D., Sc.D., LL.D., F.R.S. (EDIN.), Professor of Dermatology, University of Kansas, School of Medicine; and RICHARD L. SUTTON, JR., A.M., M.D., L.R.C.P. (EDIN.), Associate in Dermatology, University of Kansas, School of Medicine. Tenth edition, revised, enlarged and reset. Pp. 1549; 1452 illustrations and 21 color plates. St. Louis: The C. V. Mosby Company, 1939. Price, $15.00.

"Diseases of the Skin" by R. L. Sutton, Sr., has been a standard dermatologic text for about 20 years. This edition not only preserves the outstanding features of previous issues, but the father-son combination has added new ones that may establish it as the American encyclopedia of dermatologic information.

This edition not only retains the pictorial excellence for which its predecessors are known, but amplifies it by 340 new illustrations and 10 color plates. A change in type has made it possible to include 100% more text and 7000 additional references without a material increase in bulk.

Certain textual changes are noteworthy. The material has been classified on an etiologic basis and an attempt has been made to correlate cutaneous disorders with general medicine. This has called for increased space devoted to fundamental physiologic and biologic phenomena. These discussions, aided by contributions of experts in the field, are generally adequate. For ready review of certain dermatoses there are, conveniently placed, detailed lists and tables. The thoroughness of the bibliography can be judged by the section on venereal lymphogranuloma.

The authors have added valuable personal opinion and experiences to the documented statements from the literature. For example, their treatment of acne vulgaris, which cuts the average number of visits in half, demands immediate attention.

While the Reviewer has found little to complain of in this textbook, he would like to know why, if "pruritus" is as bad a diagnosis as "eczema," the authors still devote so extended and conventional a discussion to that "dermatological scrap-heap," eczema. A proper appreciation of the merits of the book can, of course, be obtained only by an examination of the book.

H. B.

THE HARVEY LECTURES, SERIES XXXIV. Delivered under the Auspices of The Harvey Society of New York, 1938–1939, under the Patronage of the New York Academy of Medicine by DRS. G. F. MARRIAN, A. A. WEICH, E. F. DUBOIS, E. J. COHN, E. A. PARK, K. LINDERSTRØM-LANG, C. H. DANFORTH, A. SZENT-GYÖRGYI. Pp. 279; illustrated. Baltimore: The Williams & Wilkins Company, 1939. Price, $4.00.

THIS latest volume of this famous series contains 8 lectures on such varied subjects as the steroid hormones, serum albumin, heat loss, proteins as chemical and biologic material, the pathology of rickets, tissue and cell enzymes, genic and hormonal factors in biologic processes, and biologic oxidations and vitamins. These latest words by leaders in their fields are indeed useful half-way stations between original reports and textbooks.

E. K.

GROSS ANATOMY. A Brief Systematic Presentation of the Macroscopic Structure of the Human Body. By A. BRAZIER HOWELL, Associate Professor of Anatomy, Johns Hopkins University School of Medicine. Pp. 403; 56 illustrations. New York: D. Appleton-Century Company, Inc., 1939. Price, $6.00.

THE author well states the dilemma of present-day teaching of anatomy in his introductory chapter: the time allotted for anatomy in the medical curriculum has been sharply decreased; the scope of the science has been broadened. The problem is to present enough of this increased fabric of anatomy in the decreased time so that the medical student may continue an orderly progress. This work is apparently intended as a substitute for the longer texts in gross anatomy. How complete this substitution is meant to be is not entirely obvious from the introduction; however, with but 56 illustrations the student would need to have other works constantly available. It seems questionable whether the problem of condensation is helped by devoting 111 pages to the muscular system and 266 pages to the rest of the body. As would be expected from the author's background, the section on muscles is the best feature of the book. The correlation with comparative anatomy is interesting and is attractively written. However, this division would seem to be of more value as collateral reading for the medical student than as text material. The correlations are toward the comparative rather than the medical side. Many of the references to comparative anatomy cannot be justified on grounds other than that of general academic interests. Some of them are definitely useful in simplifying the understanding of the human relationships. Should a short book endeavoring to cover the complete course in gross anatomy spend space to figure the forearm muscles of the iguana? These sidelights on human anatomy disappear in a large part in the presentation of the other systems in the body, where the style becomes almost breathless. There could be raised many minor objections to the presentation of anatomic facts, these sometimes representing a legitimate difference of opinion among anatomists. In view of the large amount of space devoted to the morphology of muscles, it is surprising that the function of the larynx in movements of the upper extremities is omitted.

O. B.

RECENT ADVANCES IN HÆMATOLOGY. By A. PINEY, M.D., CH.B. (BIRM.), M.R.C.P. (LOND.), Assistant Physician, St. Mary's Hospital for Women and Children, London. Pp. 312; 34 illustrations and 8 colored plates. Fourth edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1939. Price, $5.00.

THOUGH this edition has been so completely revised that it is practically a new book, it is by no means confined to "recent advances," as many

of the references will bear witness. It is rather, as stated in the first edition, an attempt to indicate "the present position of a number of hematological subjects." It doubtless will be of use to those who do not have access to recent larger and more complete works on the subject.

E. K.

DISEASES OF THE NOSE AND THROAT. By CHARLES J. IMPERATORI, M.D., F.A.C.S., Professor of Otolaryngology, New York Polyclinic Medical School and Hospital, etc., and HERMAN J. BURMAN, M.D., F.A.C.S., Adjunct Professor of Otolaryngology, New York Polyclinic Medical School and Hospital, etc. Pp. 726; 480 illustrations. Second edition, revised. Philadelphia: J. B. Lippincott Company, 1939. Price, $7.00.

IN this volume the authors present in concise form the generally accepted opinions in the field of rhinology and laryngology. The plan and form of the book follow that of the first edition published three years ago. While the text is terse and at times dogmatic, it is also explicit and thorough. The brief but adequate discussions of the embryology, anatomy and physiology of the various structures in the upper respiratory tract will appeal alike to the student, general practitioner and specialist. Considerable stress is laid upon therapeutic measures and minor technical procedures, but with the elimination of controversial matter. The illustrations are numerous, appropriate and instructive. Conscientiously assuming responsibility for systematic instruction, the authors have wisely introduced illustrations of the instruments comprising the armamentarium for various surgical procedures. Roentgen examination of the nasal accessory sinuses is treated at considerable length. The thorough and detailed treatment of such subjects as physical therapy in the nose and throat, rhinologic manifestations of general systemic diseases and laboratory aids deserves commendation. This is a well-arranged, authoritative and informative textbook.

H. S.

ELEMENTARY ANATOMY AND PHYSIOLOGY. By JAMES WHILLIS, M.D., M.S., F.R.C.S., University Reader in Anatomy, Guy's Hospital Medical School; late Lecturer in Anatomy in the University of Durham. Foreword by T. B. JOHNSTON, M.D., CH.B., Professor of Anatomy, University of London. Pp. 342; 87 illustrations prepared from original drawings by PAULINE LARIVIÉRE. Philadelphia: Lea & Febiger, 1939. Price, $3.50.

FROM the foreword by Professor Johnston and the announcement of the publisher it appears that this little book is intended for medical students as well as others beginning the study of human anatomy. The American medical student begins his study of human anatomy with a background of general biology and frequently with training in comparative anatomy. This should make superfluous the diagrammatic summary of histology. The book might be quite "effective with students in physical education and in nursing." Any short anatomy, even without physiology, must be either a dictionary-like condensation of terms or it must represent a careful selection of material. The author, obviously an experienced anatomist, has made a good selection. The presentation is handled in a conservative way, which may be the safest plan in a short anatomy. Many more pretentious works still continue to give Helmholtzian notions of ear mechanics and descriptions of the viscera based on the postmortem rather than on the living state. It is a time-honored custom to repeat illustrations, giving a different figure number. Illustration number 38 appears again as numbers 46, 55 and 60, while number 28 reappears as 53, 69 and 85. These with other repetitions reduce the total number of original figures from 87 to 69. This proportion of repetitions seems a little high. The subject matter is well organized, the definitions are clear, and the typography is such that the eye readily follows the text.

O. B.

PERIPHERAL VASCULAR DISEASES. Diagnosis and Treatment. By WILLIAM S. COLLENS, B.S., M.D., Metabolist, Chief of the Clinic for Peripheral Vascular Disease; Chief of the Diabetic Clinic, Israel Zion Hospital, Brooklyn, etc., and NATHAN D. WILENSKY, M.D., Assistant in Clinic for Peripheral Vascular Disease; Assistant in Diabetic Clinic, Israel Zion Hospital, etc. Pp. 243; 77 illustrations, 3 color plates. Springfield, Ill.: Charles C Thomas, 1939. Price, $4.50.

THE publisher properly states that "this ready reference to the facts on peripheral circulation comprehensively surveys the extensive experimental and clinical literature and supplies practical information on the diagnosis and treatment of vascular disorders in a form readily available for quick reference in private practice." Its title follows common usage of the term "peripheral *vascular* disease" to mean "peripheral *arterial* disease." Nearly one-half of the book is devoted to descriptions of diseases, the rest to treatment. The former, in this Reviewer's opinion, is more successful than the latter. The authors understandably devote considerable space to intermittent venous occlusion, their new and interesting method of treatment. However, one may be skeptical about their chief theoretical basis for its use, namely, an implication that it increases average blood flow during treatment: their measurements fail to prove the point. For the most part therapeutic management of patients is capably discussed, and suitable therapy for the individual patient properly emphasized.

H. M.

THE RECTUM AND COLON. By E. PARKER HAYDEN, A.B., M.D., F.A.C.S. Assistant in Surgery in the Harvard Medical School, Boston; Assistant Surgeon and Chief of Rectal Clinic, Massachusetts General Hospital, Boston. Pp. 434; 169 illustrations. Philadelphia: Lea & Febiger, 1939. Price, $5.50.

ANOTHER book on the rectum and colon might seem to be superfluous at the moment; nevertheless, this work by Hayden is a very practical and extremely useful one. Written almost entirely in the first person, it gives the personal experience of the author rather than an encyclopedic review of the literature. The subject is approached in the conventional manner, first a chapter on anatomy, followed by chapters on methods of examination and on the significance of the usual symptoms. In the chapter on pruritus ani the author, after mentioning the necessity for the treatment of local anal lesions, recommends various antipruritic ointments. In his clinic, reliance is placed on the injection of oil-soluble anesthetics or of alcohol in small doses in scattered areas. For anal fissure a conservative operation is outlined in which the fissure is excised and the pecten band below it incised. Dilatation of the sphincter muscle is thought to be not only unnecessary but really harmful. On prolapse of the rectum, the author cites his experience and recommends the Moschcowitz procedure.

For strictures of the rectum complicating lymphogranuloma, conservative therapy is advised until, or unless, more radical procedures are necessary. If colostomy alone does not effect a definite improvement, resection of the rectum is recommended.

In the treatment of rectal polyps, the author does not hesitate to make an incision into the colon to resect these potentially dangerous lesions. He does not mention the removal of polyps by the use of an electric snare, although the Reviewer believes this is the easiest and safest treatment of polyps which can be reached through the proctoscope. For carcinoma of the rectum, the author describes a standard abdominal perineal operation.

In reading this book, one is impressed by the fact that it is based on a personal experience. Statistics are given from the clinic at the Massachusetts General Hospital in discussing practically every one of the lesions.

One has the impression that he is visiting the clinic of the author and in this way is gaining a personal knowledge of his methods of diagnosis and treatment. The book is well printed and fairly well illustrated, mostly with line drawings and with photographs of lesions. The Reviewer can recommend this compact volume to those who are interested in the diagnosis and treatment of the disease of the anus, colon and rectum. L. F.

THE NEW INTERNATIONAL CLINICS. VOL. 3 (N.S. 2), SEPTEMBER, 1939. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia. With 17 Collaborators. Pp. 332; many illustrations, 1 colored plate, Philadelphia: J. B. Lippincott Company, 1939.

THE 16 original articles and 6 "clinics" in this number are widely diversified; the Review is on obstetric hemorrhage. The volume index gives a good survey of the material covered by this excellent quarterly.

E. K.

MATERNAL CARE AND SOME COMPLICATIONS. The Principles of Antepartum, Intrapartum, and Postpartum Care and of the Management of Some Serious Complications. Approved by The American Committee on Maternal Welfare, Inc. Edited by F. L. ADAIR, M.D. Prepared by W. C. DANFORTH, M.D., G. W. KOSMAK, M.D., R. D. MUSSEY, M.D., R. L. DE NORMANDIE, M.D., F. L. ADAIR, M.D., P. F. WILLIAMS, M.D., F. H. FALLS, M.D. Pp. 194. Chicago: The University of Chicago Press, 1939. Price, $1.50.

THIS small volume brings together under one cover the contents of two previous volumes, one on maternal care and the other on maternal care complications, both previously reviewed in the Journal (**194,** 720, 1937; **197,** 113, 1939). Its chief aim is to help reduce maternal mortality. It aims to summarize our current knowledge regarding the best technique for prenatal care and discusses the more common complications of pregnancy and labor, outlining the accepted methods for their treatment and prevention. It seems to be a good handbook for public health nurses, and for physicians who wish to keep abreast of current knowledge in this field.

D. M.

THE STORY OF SURGERY. By HARVEY GRAHAM. With a Foreword by OLIVER ST. JOHN GOGARTY. Pp. 425; 24 plates and frontispiece. New York: Doubleday, Doran & Co., Inc., 1930. Price, $3.75.

FULL advantage is taken by the pseudonymous author of this attractive book of the greater freedom permitted to a "story" than to a "history." Documentation with dates, references, and footnotes can be ignored; unsettled matters need not have both sides represented or evaluated or can readily be ignored, free rein can be given to anecdotes; completeness is not demanded and even accuracy is not as indispensable, where the chief aim is to entertain, as in a work of reference or instruction where reliability must be of prime importance. Not that the criticism of inaccuracy should be made against the author, who obviously has wide and accurate knowledge of his subject. In fact, no small part of the charm lies in the emphasis on the subjects in which the author appears to be personally interested. For this reason, perhaps, we should not object to the otherwise disproportionate space given to British contributions—both meritorious and otherwise. However, while it is good for Americans to know how much British surgery has accomplished, it is not so good for Britishers to be given such a lop-sided picture. In the four-page bibliography there is—perhaps intentionally—not one reference in a foreign language. The first 100 pages

takes us to the 13th, "greatest of centuries," whereas more than 100 are required for the 19th alone. The pictures of Paré, the Hunters, Astley Cooper, the Bells, J. Y. Simpson, and Lister are distinctly more satisfying than anything to be found in general histories. In general, we are sure that many readers will agree with Gogarty, who wrote the Foreword, "This is the best book on surgery I have ever read." E. K.

NEW BOOKS.

The Care of a Small Rat Colony. By ROLLAND J. MAIN, PH.D., Department of Physiology and Pharmacology, Medical College of Virginia, Richmond; Vitamin Assay Laboratory, Department of Agriculture and Immigration, Commonwealth of Virginia. Pp. 101; illustrated. St. Louis: The C. V. Mosby Company, 1939. Price, $2.00.

This is a reasonably complete disscussion of the details of management of a rat colony giving description of rooms, cages and other equipment, feeding, breeding, and hygenic measures. The book would have been improved by more direct descriptions and some rewriting, but may be used with profit by anyone having to do with colonies of rats, or planning to start a colony. H.R.

Sketches in Psychosomatic Medicine (Nervous and Mental Disease Monographs No. 65). By SMITH ELY JELLIFFE, M.D., Consulting Neurologist to Manhattan State and Kings Park Hospitals, New York. Pp. 155; illustrated. New York: Nervous and Mental Disease Monographs, 1939. Price, $3.00.

Electrocardiographic Patterns. Their Diagnostic and Clinical Significance. By ARLIE R. BARNES, M.D., Mayo Clinic, Rochester, Minnesota. Pp. 197; 94 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, $5.00.

Outline of Physiology. By WILLIAM R. AMBERSON, PH.D., Professor of Physiology, University of Maryland, and DIETRICH C. SMITH, PH.D., Associate Professor of Physiology, University of Maryland. Pp. 412 (double column); 177 illustrations (15 in color) by NORRIS JONES, Instructor in Scientific Illustrating, Swarthmore College. Baltimore: The William & Wilkins Company, 1939. Price, $4.00.

The Electrocardiogram and X-ray Configuration of the Heart. By ARTHUR M. MASTER, B.S., M.D., F.A.C.P., Associate in Medicine and Chief, Cardiographic Laboratory, The Mt. Sinai Hospital, New York; Associate in Medicine, The College of Physicians and Surgeons, Columbia University, New York. Pp. 222; 71 cases with 204 engravings. Philadelphia: Lea & Febiger, 1939. Price, $6.50.

Proctoscopic Examination and Diagnosis and Treatment of Diarrheas. By M. H. STREICHER, M.S., M.D., Assistant Professor of Medicine, University of Illinois, College of Medical Research and Educational Hospital, and Department of Surgery, Grant Hospital of Chicago. Pp. 149; 39 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, $3.00.

The Hospital Care of Neurosurgical Patients. By WALLACE B. HAMBY, M.D., F.A.C.S., Associate Professor of Neurology and Instructor in Surgery (Neurological Surgery), University of Buffalo School of Medicine, Buffalo. Pp. 118; 24 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, $2.00.

Manual for Diabetic Patients. By W. D. SANSUM, M.D., Chief of the Staff of The Sansum Clinic and Director of Metabolic Research of the Santa Barbara Cottage Hospital, ALFRED E. KOEHLER, PH.D., M.D., Member of the Staff of The Sansum Clinic and Member of the Metabolic Research Staff of the Santa Barbara Cottage Hospital, and RUTH BOWDEN, B.S., Dietitian of The Sansum Clinic, Santa Barbara, Calif. Pp. 227; illustrated. New York: The Macmillan Company, 1939. Price, $3.25.

Endocrine Gynecology. By E. C. HAMBLEN, B.S., M.D., F.A.C.S., Associate Professor of Obstetrics and Gynecology, Duke University School of Medicine; Gynecologist in Charge of the Endocrine Division and Sex-Endocrine Clinic, Duke University Hospital, Durham, N. C. Foreword by J. B. COLLIP, M.D., Gilman Cheney Professor of Biochemistry and Pathological Chemistry, McGill University, Montreal. Pp. 453; 169 illustrations. Springfield, Ill.: Charles C Thomas, 1939. Price, $5.50.

"The laboratory investigations of the chemistry and physiology of various glandular extracts, varying as they do from the study of very simple and essentially crude extracts to those of a high degree of purity, must of necessity—in part at least—be more or less impractical. It is quite impossible to transfer at once the results of physiological studies on various animals to man even though these results may be very clear cut and readily duplicable. Everyone who has had experience in the pure physiological field is only too well aware of the tremendous differences that exist in the responsiveness of individuals of different species to the same basic hormone treatment. Probably in no branch of endocrinology is this 'species difference' more outstanding than in the field of sex physiology. Quite irrespective then of the degree of clarity that has been attained in elucidation of the physiological or pharmacologic properties of chemically pure hormones or extracts of hormones, the clinical value—if any—of such work must be determined by clinical experiment by clinicians working alone or in collaboration with their colleagues of the laboratory. It is for this reason that this volume on endocrine gynecology by Dr. Hamblen is in my opinion very timely. . . ." (From Dr. Collip's Foreword.)

The Essentials of Medical Treatment. By DAVID MURRAY LYON, M.D., D.Sc., F.R.C.P. Ed., Professor of Clinical Medicine, The University, Edinburgh. Pp. 448; 19 illustrations. Edinburgh: Oliver & Boyd, 1939. Price, 15/-.

NEW EDITIONS.

Fractures. By PAUL B. MAGNUSON, M.D., F.A.C.S., Associate Professor of Surgery, Northwestern University Medical School; Attending Surgeon, Passavant Memorial Hospital and Wesley Memorial Hospital, Chicago. Pp. 511; 319 illustrations. Third Edition, revised and enlarged. Philadelphia: J. B. Lippincott Company, 1939. Price, $5.00.

Magnuson's new third edition of "Fractures" is thoroughly modern. It is well illustrated. The bibliography is extensive and contains important recent references. The text emphasizes the fundamental processes upon which the successful treatment of fractures must be based. This work is probably the best treatise in English dealing with fractures. G. W.

The Merck Index. An Encyclopedia for the Chemist, Pharmacist, Physician, Dentist and Veterinarian, Containing useful scientific data and other information on the physical, chemical and medicinal properties, as well as the various uses, of chemicals and drugs; also more than 4500 chemical clinico-chemical reactions, tests and reagents; formulas for preparation of culture media, fixatives and staining solutions; useful tables; antidotes for poisons; literature references. Pp. 1060. Fifth Edition. Rahway, N. J.: Merck & Co., Inc., 1940. Price, $3.00.

This valuable publication, inexpensive because it is published on a non-profit basis, contains a mass of highly useful and accurate information of the kind indicated in the subtitle. The present edition represents the biggest revision that has been undertaken since the first edition appeared in 1889, almost doubling the size of the fourth edition (1930). It will be of use to physician, dentist, veterinarian, and to the laboratory worker as well as the clinician. E. K.

Human Helminthology. A Manual for Physicians, Sanitarians and Medical Zoölogists. By ERNEST CARROLL FAUST, A.B., M.A., PH.D., Professor of Parasitology and Director of Laboratories, Department of Tropical Medicine, Tulane University of Louisiana, New Orleans. Pp. 780; 302 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1939. Price, $8.50.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE.

UNDER THE CHARGE OF
JOHN H. MUSSER, M.D.
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

A CLASSIFICATION OF HEMORRHAGIC DISEASES DUE TO DEFECTS IN THE COAGULATION MECHANISM OF THE BLOOD.

BASED ON RECENTLY PUBLISHED STUDIES.

GREAT strides have been made during the past few years in the study of the coagulation of blood. Much knowledge has rapidly accumulated, and has found immediate clinical application. No comprehensive attempt, however, has been made to organize this new information or to utilize it for outlining a classification of hemorrhagic diseases which the clinician can use as a guide both in diagnosis and in treatment. The object of this review is to develop such a classification.

It is fairly well recognized as Kugelmass[31] pointed out, and as Madison and Squier[33] have recently reëmphasized that the body has a dual defense against hemorrhage: the first being the coagulability of the blood, and the second, the vascular response to trauma and injury. Surprisingly, the latter factor is in all probability involved in many more bleeding conditions than is the defective coagulation of blood. The importance of the vascular defense is strikingly illustrated by a case recently described by Macfarlane.[32] The blood of his patient was completely lacking in fibrinogen, presumably from birth, and therefore could not clot. Nevertheless this patient had reached the age of 8 years without encountering any hemorrhage that could not be controlled.

So little is known about the fundamental factors of the vascular response that one can only recognize the existence of a group of hemorrhagic diseases, notably the purpuras, in which it is fairly certain that the basic defect is vascular. Madison and Squier hold that a group of hemorrhagic diseases are of a mixed type, *i. e.*, partly vascular and partly involving dysfunction of coagulation. Until further trenchant knowledge on this subject has accumulated, it seems futile to attempt any extensive discussion or to offer any elaborate classification of these diseases.

In regard to the first defense mechanism against hemorrhage, namely, the coagulation of the blood, sufficient data are now available to allow the formulation of a satisfactory theory to explain the coagulation mech-

anism and to use this as the basis for a classification of hemorrhagic diseases.

As the culmination of the researches begun by Alexander Schmidt and extended by the work of Hammarsten, Arthus and Pages, Pekelharing, Fuld and Spiro, Bordet, Howell, Morawitz and others,[27b] there has evolved a simple theory for the explanation of the coagulation mechanism, which Wöhlisch[71b] has appropriately named the classical theory of coagulation. It is concisely expressed in the form of two equations:

Prothrombin + thromboplastin + calcium = thrombin

Fibrinogen + thrombin = fibrin

It can be seen that the clotting process consists of two distinct steps: first, the formation of thrombin; and secondly, the conversion of fibrinogen by thrombin to fibrin. It is important to note that only four primary factors are required for the clotting of blood, namely, prothrombin, thromboplastin, calcium, and fibrinogen; and obviously a deficiency of any one of these will wholly inhibit or markedly delay the coagulation of blood. It is therefore desirable to summarize briefly the most important facts known about these four agents in order that their significance in the various hemorrhagic diseases can be fully understood.

Prothrombin. This agent is the precursor or mother substance of thrombin, the active coagulating enzyme. It is believed to have the nature of a proenzyme, is closely associated with the serum protein, globulin, is inactivated at 60° C., and is removed from plasma by alumina cream, magnesium hydroxide, and other similar adsorbing agents. It is apparently found exclusively in the plasma and is not derived from the platelets as was formerly assumed.[14a] The view that prothrombin is combined with an antiprothrombin similar to or identical with heparin has been largely abandoned, especially since no evidence can be found that normal blood contains any anticoagulant such as heparin.[47b] Several methods for the determination of prothrombin have been developed. Quick's[47a,49] method is based on the clotting time of oxalated plasma after adding an excess of thromboplastin and a fixed amount of calcium. From the clotting time, the prothrombin can be determined by means of a chart prepared by the author. In a second method (Warner, Brinkhous and Smith[67]) the plasma is diluted, after which the prothrombin is converted to thrombin. From the dilution required to obtain a thrombin solution which will clot a preparation of fibrinogen in 15 seconds, the concentration of prothrombin is empirically calculated. An indirect method for determining prothrombin is employed by Dam and Glavind.[11a] It consists in finding the minimum amount of thromboplastin required to clot, in 3 minutes, blood to which a fixed quantity of heparin has been added.

Studies made on the prothrombin content of normal blood disclose two interesting findings: first, the constancy of the prothrombin level, and second, the large excess which is many times more than the physiologic requirements. It has been shown by Quick, Stanley-Brown, and Bancroft[50] that 80% of the prothrombin can be lost before the coagulation time is appreciably prolonged; and clinically it has been found that serious hemorrhage does not occur until the prothrombin sinks below 20%.[6b,47f,60]

Thromboplastin. This substance has the function of converting prothrombin into active thrombin. In this reaction ionized calcium is essential. Whether thromboplastin merely activates prothrombin, or whether it actually unites chemically is not known. Recently Eagle and Harris[15] have demonstrated that trypsin can change prothrombin to thrombin. This finding suggests the possibility that the action of thromboplastin may likewise be that of an activating enzyme. If this can be proved, the term thrombokinase should replace thromboplastin. In the past many other names have been applied to this agent, such as tissue extract, tissue fibrinogen, cytocyme, thrombocyme, cephalin, and platelet factor.

Thromboplastin is widely distributed in the body as an intracellular substance. In the blood, it occurs locked up in the platelets and perhaps is present also in the leukocytes. Certain tissues, notably the brain, lungs, and thymus, are particularly rich in thromboplastin. It apparently never occurs free, but is liberated whenever tissue cells are injured or ruptured. In blood uncontaminated by tissue juices, the thromboplastin is derived solely from the platelets. The liberation of thromboplastin from platelets, therefore, appears to be the prime factor in determining the clotting time of blood obtained by venipuncture. The slowness with which thromboplastin is liberated is illustrated by this simple experiment: On placing 1 cc. of blood obtained by venipuncture in a small test tube, it will remain liquid for 4 to 8 minutes, whereas if the same quantity of blood is mixed with a drop of an active thromboplastin solution, coagulation occurs in less than 20 seconds. Thromboplastin is fairly resistant to heat. Even on boiling for several minutes, not all of its activity is lost. Oxidation, however, destroys its potency, perhaps because of the presence of unsaturated lipoids in its molecule. It is widely accepted that cephalin is a constituent of the thromboplastin complex.

Calcium. For the conversion of prothrombin to thrombin, ionized calcium is essential. Whether this element is present in the thrombin molecule has not been decisively answered, but it appears certain that the presence of calcium is not needed for the action of thrombin on fibrinogen. This is the original view of Hammarsten which recently has received strong support from the careful research of Weitnauer and Wöhlisch.[70]

Calcium appears to play an important part in the lysis of platelets. Early workers observed the preservation of platelets in decalcified blood, and Ferguson[18] has convincingly demonstrated that calcium alters the platelet in such a manner that the osmotic pressure within the cell is increased thus causing it to take up water to the point of disruption. The writer recently has observed that goose blood, which will remain liquid for days, can be made to clot in a few minutes by adding a small amount of calcium chloride.

Fibrinogen. This exceedingly labile plasma protein has the property of being converted from a colloidal solution or sol to an insoluble gel by the action of thrombin. In this process, the fibrin forms fine needles or threads which enmesh the cellular constituents of the blood. Tocantins[64] has shown that platelets will attach themselves to the shaft of these fibrin threads, and in some inexplicable way cause these fibrin

strands to bend and twist thereby effecting a compression of the fibrin mass which is grossly recognized as clot retraction.

Not only do the platelets bring about the contraction of the clot, but also in some obscure manner they increase the adhesiveness of the fibrin to surfaces with which it comes in contact. The importance of this in hemostasis is obvious. The clot within the lumen of a severed blood-vessel by adhering tightly to the wall will bring about by its contraction a mechanical constriction of the blood-vessel.

Fibrinogen occurs not only in the plasma, but also in lymph, chyle, exudates and transudates. Undoubtedly this protein plays as important a part in tissue repair work as it does in coagulation.

Thrombin. This substance is not a primary factor, but a resultant from the interreaction of prothrombin, calcium and thromboplastin. Most investigators are accepting the view that thrombin is an enzyme which acts specifically on fibrinogen. An excellent summary of the evidence for the hypothesis has been presented by Eagle.[14c] Certain snake venoms such as that of the tiger snake contain a substance similar or identical to thrombin, which is responsible for their powerful coagulant action. Recently Quick[47a] has shown that thrombin is inactivated by serum albumin, and he has concluded that this serum protein is the normal antithrombin of the blood which is responsible for the rapid disappearance of thrombic activity in fresh serum. It should be noted that serum albumin does not inhibit the coagulation of fibrinogen, but acts only after the conversion to fibrin has been complete.

For a comprehensive understanding of the coagulation problem, it is essential to know that the clotting time is proportional to the concentration of thrombin. Fuld[20] expressed the relationship between the clotting time and the concentration of thrombin as follows: $\log \frac{t_1}{t_2} = .0585 \log \frac{y_2}{y_1}$ (t = clotting time; y = concentration of thrombin). Martin[34] stated it more simply: ty = a constant. Barrett[4] more recently has elaborated on Martin's equation. These equations unfortunately are not suitable for practical application. Recently the author found that it was possible to prepare a thrombin solution having a high and constant activity.[47b] When one part of this solution is mixed with two parts of oxalated plasma, a clot is formed in exactly 3 seconds. By progressively diluting the thrombin solution, the clotting time is increasingly retarded, and if the clotting times are plotted against the concentrations of thrombin, a curve is obtained, which over a wide range including the crucial portion of the curve corresponds to the equation: $c.t. = a + \frac{k}{c}$. (c.t. = clotting time; c = concentration of thrombin; a and k constants having the value 2.38 and 88, respectively, provided the thrombin solution which causes clotting in 3 seconds is taken as 100%.) By means of such a standard thrombin solution, any blood can be tested for the presence of heparin or similar antithrombogenic agents as Quick[47c] has, for example, demonstrated in the plasma after peptone shock.

On the basis that prothrombin, thromboplastin, calcium and fibrinogen are essential for the clotting of blood, and furthermore that coagula-

tion can be inhibited by the presence of natural anticoagulants such as heparin in plasma, a simple classification of hemorrhagic diseases (exclusive of those due to vascular disturbance) can be outlined. Absence or marked deficiency of any one of the primary factors gives rise to four potential classes of bleeding diseases, and a fifth type arises when a sudden liberation of heparin or a heparin-like substance occurs into the blood stream. An attempt will be made to group the common hemorrhagic diseases into these 5 classes. Although prothrombin and thromboplastin are treated as single substances, due cognizance is given to the possibility that these agents, like complement, may be made up of several components. If this be found, the classification would merely need to be enlarged, but not fundamentally altered.

1. **Diminished Prothrombin.** A. Deficiency of Vitamin K. (*a*) *Dietary Origin.* In 1934 Dam and Schönheyder[12] in Denmark, and the next year Almquist and Stockstad[2a] in this country demonstrated that a hemorrhagic disease could be produced in chicks fed a diet complete in all respects except for a new unknown factor, which was fat soluble. Dam named this new substance vitamin K. Almquist found that an ether extract of alfalfa had a high concentration of this vitamin and readily cured the bleeding dyscrasia in chicks. In 1936 Dam, Schönheyder and Tage-Hansen[13] found that they could not isolate prothrombin from the blood of chicks kept on a vitamin-K-poor diet, and Quick[47e] a few months later showed that the prothrombin began to diminish 4 days after removing vitamin K from the diet, and could be reduced to less than 10% of normal in less than 3 weeks. He further found that the prothrombin was promptly restored to normal by adding 2% alfalfa meal to the diet. These results definitely demonstrated that vitamin K is necessary for the synthesis of prothrombin in the chick. Recently, Greaves[22] succeeded in developing a hemorrhagic condition in rats solely by depriving the animal of vitamin K. The great majority of the rats, however, retained their prothrombin level even after prolonged deprivation of this food factor. It is well known as the result of Almquist's studies[2b] that vitamin K is synthesized by the bacteria in the intestinal tract, and this undoubtedly explains the difficulty of producing a hypoprothrombinemia by dietary means alone. It is therefore doubtful whether in the adult an inadequate diet by itself can ever affect the prothrombin concentration. There is reason to believe, however, that the hemorrhagic diathesis of the newborn may be caused purely by a lack of vitamin K and the disease therefore will be discussed under this heading.

Hemorrhagic Disease of the Newborn. It now appears to be quite certain that a deficiency of prothrombin is the cause of the hemorrhagic disease in the newborn. Brinkhous, Smith and Warner[6a] reported 1 case in which the prothrombin was extremely low, and recently Waddell, Guerry, Bray and Kelley[65] published 2 more cases in which the prothrombin likewise was greatly reduced. Since the latter 2 babies responded promptly to vitamin K administration, one can conclude that deficiency of this vitamin exists in certain babies. Brinkhous *et al.*, concluded that the prothrombin in newborn babies is normally less than 40% of the adult concentration, does not exceed this level up to the age of 2 weeks, and does not attain the normal level until at the end of the

first year. Their study is rather unsatisfactory since only 3 babies less than 11 days old (5, 8 and 8 days) are included in the series which they report. Quick and Grossman[48] were unable to confirm the findings of Brinkhous and his associates. On the contrary, they found that the prothrombin of babies 3 days or older was with few exceptions entirely normal. Furthermore, in babies 6 hours old, the prothrombin likewise was not greatly reduced. The values ranged from 70 to 80%. Surprisingly, however, in 2 out of 3 babies that were 1 day old, a very drastic reduction in the prothrombin was found, but this low level appeared to be of short duration since a prompt spontaneous rise occurs which in 1 or 2 days brings the prothrombin back to normal. These results have been confirmed by the Iowa investigators[42] with the use of Quick's prothrombin method. These findings greatly aid in understanding the nature of the hemorrhagic diathesis of the newborn. Apparently no reserve of prothrombin is built up in the fetus, and in 24 hours after birth this clotting factor may drop to a dangerously low level. Normally, a prompt spontaneous recovery of the prothrombin concentration occurs. If this is delayed, the typical hemorrhagic disease of the newborn develops. Vitamin K readily cures the disease. The source of the vitamin K which brings about the normal restoration of prothrombin remains to be found. As the baby consumes scarcely any food up to the time recovery is noted, an outside supply is improbable. Since vitamin K is synthesized by bacterial action within the intestine, it is logical to conclude that as soon as the baby takes water or food it infects the intestinal contents which at birth are sterile. With the establishment of an intestinal flora, the synthesis of vitamin K begins, and its absorption with the aid of bile ends the danger of bleeding. It seems not unlikely that the most important source of vitamin K in both infants and adults may be the products produced by bacteria within the upper intestinal tract.

(*b*) *Faulty Absorption.* It is well known that bile fistula dogs can develop spontaneous hemorrhage.[26] Hawkins and Brinkhous[25] found that the prothrombin was greatly diminished in these animals. More recently Greaves and Schmidt[23] showed that the prothrombin could be markedly lowered by either ligation of the bile duct or by making a biliary fistula. The prothrombin level in such rats could readily be elevated by either massive doses of vitamin K or by feeding bile salts. The suggestion of Quick[47e] that the absence of bile in the intestine leads to impaired absorption of vitamin K with a resultant lowering of plasma prothrombin is also the conclusion of subsequent workers.

It is highly improbable that a prothrombin deficiency can be produced in the adult by dietary means alone. Thus far a reduction of prothrombin has been observed only in biliary tract disease. Quick, Stanley-Brown and Bancroft in 1935[50] reported that in certain cases of jaundice a severe diminution of prothrombin was found. In 1938 these findings were corroborated by Brinkhous, Smith and Warner,[6b] and by Snell and others of the Mayo Clinic.[59] Both groups of investigators demonstrated the efficacy of treating this deficiency condition with vitamin K and bile salts. During the past year others[11b,38,63] have added cases of biliary disease including biliary fistula in which the hemorrhagic diathesis was successfully treated with bile and a vitamin K concentrate.

(*c*) *Sprue.* Engel[17] has reported that the hemorrhagic diathesis observed in sprue may be attributed to lack of vitamin K. It is highly probably that a low prothrombin concentration will also be found in various other conditions in which one may expect inadequate absorption of fat soluble vitamins. This conclusion has since the completion of this paper been clinically confirmed by Clark, Dixon, Butt and Snell.[10] They observed a deficiency of prothrombin in sprue, intestinal polyposis, chronic ulcerative colitis, gastrocolic fistula, and other conditions.

B. Liver Damage. A tendency to bleed often occurs in severe liver injury, and is frequently observed in acute yellow atrophy. In these conditions the fibrinogen is greatly diminished and it has been quite generally assumed that this accounted for the hemorrhagic condition. Recently Smith, Warner and Brinkhous[58] found that when a dog was subjected to prolonged chloroform anesthesia, a marked drop in prothrombin occurred which was far more abrupt and severe than the decrease in fibrinogen. Quick[47f] likewise found that he was able by this means to reduce the prothrombin to less than 5% of normal. In view of these findings, it seems reasonable to postulate that in extensive parenchymatous damage of the liver, the cause of bleeding is the reduced concentration of prothrombin, and it seems safe to predict that further study will disclose that the blood in acute yellow atrophy is markedly deficient in prothrombin. Warner[66] was able to reduce the prothrombin level by partial hepatectomy, which further emphasizes the important rôle played by the liver. Warren and Rhoads[68] found that after total hepatectomy in the dog, a rapid decline occurred in the prothrombin of the plasma. These authors concluded from their results that the liver is essential for the formation of prothrombin.

The effect of liver damage on the prothrombin concentration of the blood is perhaps of greatest significance in the jaundiced patient. There are great variations in the response that patients with diminished prothrombin show to vitamin K therapy. A few react promptly and often even spectacularly while others respond sluggishly. Assuredly an adequate supply of vitamin K and good absorption are not the only factors. Utilization of this food accessory substance is equally important. It seems permissible to assume that the liver is concerned in converting vitamin K into the prothrombin component; consequently, if liver function is seriously impaired, the synthesis of prothrombin is decreased even though enough of the vitamin is consumed to fulfill adequately the normal metabolic demands. In other words, if impaired liver function occurs, more vitamin K is required to compensate for the faulty utilization. In the jaundiced patient, the diminished prothrombin may thus be due either to inadequate absorption or to faulty utilization; and perhaps in many cases both factors are present.

C. Sweet Clover Disease. Cattle which are fed sweet clover hay that has been spoiled are apt to develop a severe hemorrhagic disease which has considerable economic significance. Frequently simple operations such as castrating bull calves, and dehorning cattle, are followed by uncontrollable hemorrhage. Roderick[54] who was the first to investigate this disease thoroughly, observed that the prothrombin was decreased. This finding was confirmed by Quick,[47e] who studied the decrease of this clotting factor quantitatively. It is quite certain that

the sole coagulation defect in this disease is a severe reduction of the prothrombin of the blood, but how this is brought about is not known. Since the prothrombin is promptly restored as soon as the toxic hay is replaced by a normal diet, it seems rather improbable that any significant organic damage has occurred. It seems more likely that a toxic principle found in this hay directly inactivates the prothrombin. If this assumption is correct, one must recognize the possibility that similar toxic agents may perhaps be encountered clinically which may attack the prothrombin of the blood. At present, however, no human disease is known which resembles the condition produced by feeding toxic sweet clover to rabbits and cattle.

2. Calcium Deficiency. Although calcium plays an exceedingly important part in the coagulation mechanism, it is very doubtful whether even the extreme variations in its concentration which occur pathologically can influence the clotting time. *In vitro* experiments indicate that the concentration of calcium within a fairly wide range has no significant influence on the rate of coagulation. No hemorrhagic diathesis is associated with parathyroprivia although in this condition the calcium may reach the lowest concentration compatible with life. Ravdin, Riegel and Morrison[52] found that a patient in parathyroid tetany with a serum calcium of 4.6 mg. per 100 cc. had a normal coagulation time. At present, therefore, it is not possible to name any clinical or experimental bleeding condition that can be attributed to a deficiency of calcium. Nevertheless, much remains to be known. The influence of ionized and un-ionized calcium on the stability of platelets may perhaps be of much greater clinical importance than one would suspect.

3. Thromboplastin Deficiency. Thromboplastin appears to be widely distributed in the body as an intracellular substance, but only the fraction locked up in the platelet seems to be responsible for bringing about dysfunction of the coagulation process. In order for blood to clot, free or available thromboplastin is required. If there is no contamination of tissue juices, the only source is the platelet. An inadequate supply of thromboplastin obviously may arise in three ways: 1. Reduction in the number of platelets. 2. Platelets deficient in thromboplastin. 3. Abnormal resistance of platelets to lysis.

A priori it would seem that one can classify thrombocytopenia as a hemorrhagic disease on the basis of decreased thromboplastin. No doubt when prolonged coagulation in this disease is encountered, it may well be the result of thromboplastin deficiency. Howell[27c] has studied such a patient, who had a platelet count of 64,000 and also had a prolonged coagulation time. The platelet appears to have another function, a specific effect on capillary permeability, and in the purpuras this second function far overshadows the thromboplastin factor.

Apparently a marked reduction in platelets can occur without bringing about a delay in the clotting time. Interestingly a number of patients have been studied who may shift from a condition of hemophilia with a normal number of platelets but a delayed coagulation time to a purpuric syndrome with a marked thrombocytopenia but a normal clotting time. Such cases have been described by Pickering[45] and by Minot and Lee.[36] The information concerning the qualitative and quantitative variations of thromboplastin in the platelet is too conflicting and uncertain to be

of any specific value in differentiating and classifying hemorrhagic diseases. The importance of abnormal stability of platelets will be considered in the following section, "Hemophilia."

A. Hemophilia. An adequate discussion of this subject would go well beyond the confines of this paper. An attempt will be made merely to show how much of the experimental evidence points to the possibility that in hemophilia the platelets are abnormally resistant and therefore yield thromboplastin too slowly to bring about coagulation within the normal time. The fact that hemophilic blood will always ultimately clot shows that no essential factor is absent.

What are the findings that suggest an inadequate quantity of thromboplastin? In 1908 Morawitz and Lossen[37] found that hemophilic blood clotted extraordinarily rapidly when an extract of kidney tissue was added. Kottmann and Lidsky[30] achieved the same rapid clotting with a liver extract. Schlossmann[57] and Mills[35] likewise demonstrated the effectiveness of tissue extracts. Since the tissue extracts of organs are almost always badly contaminated with prothrombin or thrombin, these earlier experiments were not entirely satisfactory. Quick, Stanley-Brown and Bancroft[50] succeeded in preparing a highly active preparation of thromboplastin from rabbit brain, which was free from prothrombin and thrombin. On adding a measured amount of this active material to hemophilic blood and to normal blood, both coagulated with equal rapidity. From these results Quick[47a] concluded: "This suggests that in hemophilia the prothrombin is normal in quantity and quality but thromboplastin is deficient."

Were prothrombin qualitatively altered, *i. e.*, less reactive as Addis and, more recently, Eagle[14b] have postulated, one would expect that the action of thromboplastin would not be as effective on hemophilic as on blood containing normal prothrombin. Howell[27c] in a recent comprehensive study on hemophilia has pointed out the probable error in the experimental studies of Addis and Eagle on which their conclusion is based. As the result of his latest studies, Howell concludes: "As far as blood is concerned we may conclude that one real difference between normal and hemophilic blood is that the latter contains less thromboplastin in its plasma. There may be other differences, but they have not been discovered. It would seem permissible to assume that this deficiency is sufficient to explain the prolonged clotting time of hemophilic blood."

Since thromboplastin takes on a new significance in the consideration of the basic defect in hemophilia, attention must be directed to the important source of this clotting factor, namely, to the platelet. Since the thromboplastin is locked up in the platelet and becomes available only after the latter disintegrates, the importance of the stability of these cellular elements is obvious. It seems that the environment rather than the platelet itself is the real determinant. Howell states that when platelets are removed from their natural environment, freed from plasma, and suspended in saline solution, they become exceedingly resistant, and do not break down when they come in contact with a foreign surface. Clearly this suggests that some factor in plasma governs the resistance of the platelet in plasma, and as a working hypothesis one might venture to suggest that this labilizing influence is absent or depressed in hemo-

philia. In support of this is the finding of Govaerts and Grata[21] that platelets of hemophilic blood disintegrate normally in non-hemophilic plasma. Fonio,[19] however, found that washed normal platelets disintegrated as rapidly in hemophilic plasma, whereas the washed hemophilic platelets appeared more stable. More studies are required before one can definitely decide whether the abnormal stability of the platelet resides in the cell itself, or in its environment. It is fairly generally accepted, however, that the platelet is more resistant in hemophilia, and many investigators, particularly Sahli,[56] Wöhlisch,[71a] Minot and Lee,[36] Fonio,[19] Howell and Cekada,[28] and Opitz and Zweig[41] have furnished experimental evidence to support this conclusion.

It seems justifiable to classify hemophilia as a hemorrhagic disease caused by an insufficiently available supply of thromboplastin. No attempt will be made to discuss the important work of Patek and Stetson,[43] Pohle and Taylor,[46] Bendien and Van Creveld.[5] There is nothing in their findings which alters the general concept of hemophilia that has been presented.

4. Fibrinogen Deficiency. A. Acquired Fibrinogenopenia. The normal range of fibrinogen is roughly 0.2 to 0.4%, but may fluctuate beyond these limits. Since fibrinogen is essentially a passive agent in the coagulation process, its concentration within a wide range has no significant influence on the clotting time. Obviously, however, the density of the clot depends on the amount of fibrinogen in the blood, but even in this respect there is a wide margin of safety, for the fibrinogen may be greatly diminished, to as low as 0.02%, according to Risak,[53] without causing any evidence of a hemorrhagic tendency. As a matter of fact, a low fibrinogen with normal adhesiveness and clot retractive power is far superior hemostatically to a fibrinogen normal in amount but lacking these two essential properties. Nevertheless, a critical concentration must exist below which imperfect clot formation occurs, but no satisfactory determination of this level has been made.

Low fibrinogen may result from nutrition deficiency. Ham and Curtis[24] have shown that this may occur in pernicious anemia, scurvy and pellagra, thus confirming earlier work by Starlinger and Winands.[61] A marked fibrinogenopenia may be sometimes found in myelogenous leukemia, myelogenic sarcoma, and other diseases involving the blood forming organs.[53] Of great significance is the report by Jurgens and Trautwine[29] of a patient whose blood was completely incoagulable due to the absence of fibrinogen. On autopsy it was found that the liver was normal, but a widespread destruction of bone marrow had occurred due to metastasis from a prostatic carcinoma. Opitz and Silbermann[40] reported a similar case caused by generalized tuberculosis.

Low fibrinogen values are found in severe liver damage, especially in acute yellow atrophy. It is nevertheless doubtful whether the fibrinogenopenia is the actual cause of the bleeding which is frequently observed. As has already been stated, liver injury is usually followed by a drastic reduction of the prothrombin, and it seems certain that this latter factor is by far the more important in bringing about a hemorrhagic tendency. Smith, Warner and Brinkhous[58] showed that in dogs poisoned with chloroform, the prothrombin dropped more abruptly, to a greater degree, and for a longer period, than did the fibrinogen concentration.

Certain snake venoms such as that of the black snake of Australia and the tiger snake will clot fibrinogen *in vivo*, thus causing its complete disappearance from the blood.[55] This causes the incoagulability of the blood observed after a snake bite by these species. The hemorrhagic phase, however, is of short duration since fibrinogen again appears in the blood after several hours.

B. Congenital Fibrinogenopenia. Consistent and complete absence of fibrinogen from the blood due presumably to an inborn anabolic error has been reported only 3 times. Rabe and Salamon[51] described the first case in 1921, and the following year Opitz and Frei[39] published the second. Last year Macfarlane[32] presented a detailed case report of a third patient with congenital absence of fibrinogen. The first and third children were over 8 years old, indicating the importance of the vascular defense mechanism against hemorrhage, since in neither case was there any evidence that the blood was at any time coagulable. In the first patient, the platelets were normal in number but appeared resistant, whereas the third had a thrombocytopenia up to the age of 8. Macfarlane believes that the defect is inherited and has a recessive character. The parents of his patient were first cousins. Consanguinity of the paternal grandparents of their patient was reported by Rabe and Salamon.

It is interesting to note, but difficult to understand, that in spite of the complete incoagulability of the blood the 2 patients that lived to be 8 years of age seemed to have escaped serious incapacitating hemorrhages, such as bleeding into joints, more successfully than is usually the case in severe hemophilia.

The differential diagnosis between true hemophilia and fibrinogenopenia offers no difficulty. The simple addition of a few drops of thromboplastin solution such as is used in Smith's or Quick's prothrombin method will cause hemophilic blood to clot promptly, but will have no action on the second blood.

5. Anticoagulants. The presence in the blood of any agent which neutralizes or inactivates one of the four factors required for coagulation can hypothetically bring about a hemorrhagic state. The antithrombins and possibly the antiprothrombins, however, are the only ones which need to be considered clinically. There is no evidence that the blood ever contains any substance which renders fibrinogen incoagulable, or neutralizes thromboplastin. Likewise, the agents which prevent clotting by removing ionized calcium, such as the soluble oxalates and citrates, although very valuable for *in vitro* experiments are not encountered clinically as causes of hemorrhage. Except for the use of sodium citrate in transfusion, no extensive use of these reagents to inhibit coagulation *in vivo* is made at present.

In considering the antithrombins, it is important to recognize that blood contains a natural neutralizing agent of thrombin, which Quick[47g] has shown to be either serum albumin itself or a substance closely associated with this protein fraction. Both fibrinogen and albumin have an affinity for thrombin, but the former is much greater. The fibrinogen-thrombin complex is very likely an intermediary step in the conversion of fibrinogen to fibrin. As soon as fibrin is formed, thrombin is reliberated to react with more fibrinogen, and only when coagulation is

complete does the albumin get a chance to combine and thereby neutralize thrombin. Quick has furthermore offered experimental evidence to show that heparin, which is *per se* not an antithrombin,[47d] acts by intensifying the antithrombin activity of serum albumin. By adding heparin to blood, a strong anticoagulant presumably an albumin-heparin complex is formed, which combines with thrombin before the latter can react with fibrinogen. It is entirely probable that this albumin-heparin complex likewise combines with prothrombin, thus preventing the formation of thrombin. Such a hypothesis will explain the recent findings of Brinkhous, Smith, Warner and Seegers[7] that heparin in conjunction with an unidentified substance of the plasma prevents the formation of thrombin. It is logical to speculate that this unknown factor is serum albumin. Due to the work of Best and his co-workers, heparin is now widely used to make blood less coagulable as a prophylaxis against thrombosis.

It is unlikely that heparin is present in normal blood. Quick[47b] has developed a titration method for detecting heparin in plasma, which is easily sensitive to less than 1 mg. of crude heparin per 100 cc. of blood. He was unable to find any trace of heparin in normal plasma. There is, however, good evidence that heparin or a closely related substance appears in the blood both in peptone and in anaphylactic shock. As the result of his studies, Howell[27a] attributed the incoagulability of the blood in peptone shock to heparin. Quick[47c] confirmed Howell's work and showed that the blood contained the equivalent of 1 mg. or more crude heparin per 100 cc. 5 minutes after the injection of peptone. Eagle, Johnston and Ravdin[16] demonstrated that anaphylactic shock was regularly associated with the presence of increased amounts of antithrombin in the blood. They did not attempt to correlate their findings with heparin. Earlier workers, particularly Pepper and Krumbhaar[44] and Zunz and La Barre,[72] had likewise come to the conclusion that the antithrombin was responsible for the delayed clotting in anaphylactic shock. Recently Waters, Markowitz and Jaques[69] employing the finding of Chargaff and Olson[9] that protamine completely removes heparin from blood, were able to determine quantitatively the heparin in the blood after both peptone and anaphylactic shock. They further found that no antithrombin occurred in a shocked liverless dog, and concluded that this organ was responsible for the outpouring of heparin. Thus, the incoagulability of blood in the two experimental types of shock can be attributed to the sudden liberation of heparin into the blood. It seems justifiable to predict that if the blood of a patient in anaphylactic shock be analyzed it likewise will show the presence of heparin.

Many other substances are known which can inhibit the activity of thrombin. Of these, certain sulphur compounds such as cysteine, methionine, taurine and taurocholic acid, have been shown by Sterner and Medes[62] to act as anticoagulants. Earlier Carr and Foote[8] attributed the hemorrhagic tendency in jaundice to cysteine. With the advent of vitamin K, this hypothesis has been largely abandoned. It seems questionable whether these sulphur compounds or any other anticoagulants, save heparin, need to be considered as causes of hemorrhagic conditions encountered clinically.

Epitomizing the discussion of the hemorrhagic diseases caused by defects in the coagulation mechanism, the following outline for their classification is offered:

I. Diminished prothrombin (Prothrombinopenia).
  A. Lack of vitamin K:
    (*a*) Dietary origin—absence of bacteria in intestines; (1) hemorrhagic disease of the newborn. (*b*) Faulty absorption—lack of bile salts; (1) obstructive jaundice; (2) biliary fistula; (3) sprue.
  B. Liver damage—faulty utilization of vitamin K:
    (*a*) Post-anesthesia liver damage; (*b*) chloroform poisoning; (*c*) acute yellow atrophy.
  C. Toxins:
    (*a*) Toxic sweet clover disease of cattle.
II. Changes in concentration of calcium in blood. (No clinical or experimental hemorrhagic conditions known which are attributable to changes of the calcium concentration.)
III. Deficiency of thromboplastin (Thromboplastinopenia).
  A. Diminished number of platelets:
    (*a*) Thrombocytopenia (this disease is best classified under "defective vascular response" since the vascular dysfunction predominates).
  B. Increased resistance of platelets:
    (*a*) Hemophilia.
IV. Decreased fibrinogen (Fibrinogenopenia).
  A. Acquired fibrinogenopenia:
    (*a*) Nutritional deficiencies; (*b*)diseases of blood forming organs; (*c*) severe liver damage; (*d*) snake bites (Black snake of Australia).
  B. Congenital.
V. Anticoagulants in the blood.
  A. Liberation of heparin into the blood:
    (*a*) Peptone shock; (*b*) anaphylactic shock.

On the basis of this classification, a satisfactory diagnosis of a hemorrhagic disease can be made. A prolonged coagulation time by the Lee White method may be due to diminished prothrombin, thromboplastin, or the presence in the blood of an anticoagulant such as heparin. If the blood ultimately clots, the presence of fibrinogen is established. The concentration of prothrombin may be readily determined by one of the quantitative methods mentioned.[49,67] The presence of an antithrombin in the blood may be detected and even quantitatively estimated by the thrombin titration method.[47c] Hemophilia can be readily diagnosed, for the prothrombin will be found normal even though the clotting time may be exceedingly delayed. The clotting time of recalcified plasma, as employed by Bancroft, Stanley-Brown and Quick,[3] is particularly useful, especially with the recent modification proposed by Quick.[47b] The latter found that the clotting time of recalcified oxalated normal plasma was not very much influenced by the speed of centrifugation employed in obtaining the plasma. With hemophilic blood, however, the rate of centrifuging the blood so strikingly affected the clotting time that he has suggested using the procedure as a new

test for hemophilia. A quantitative determination of fibrinogen and of serum calcium completes the required investigation to determine a defect in the coagulation mechanism.

If no abnormality of the clotting process can be found, the hemorrhagic disease must be considered from the vascular point of view. Three tests are particularly useful: 1, The Duke bleeding time. 2, The capillary resistance test of Rumpel-Leede or Hess. 3, The clot retraction time. These tests are usually positive only in hemorrhagic diseases, such as the purpuras, in most of which the fundamental defect appears to be vascular.

Summary. A clinical classification of the hemorrhagic diseases is presented which is based on the coagulation theory of Morawitz. A disturbance of the coagulation mechanism can be brought about by diminished prothrombin, delayed liberation of thromboplastin, absence of fibrinogen, and the presence of antithrombins such as heparin in the blood. These defects are responsible for a large number of well known hemorrhagic diseases. The approach to the diagnosis of a hemorrhagic disease is very briefly indicated.

ARMAND J. QUICK, PH.D., M.D.

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CARDIOSPASM OR ACHALASIA OF THE ESOPHAGUS.

The terms cardiospasm and achalasia have been used generally to cover the same clinical picture, the differences in point of view on etiology accounting for the different names. Since there has been little agreement concerning the mechanisms and etiology of the condition, one finds a variety of terms, often based upon the etiologic concepts of the author, in the literature. These include idiopathic dilatation of the esophagus, phrenospasm, esophagectasia, hiatal esophagismus, megaloesophagus, simple ectasia of the esophagus, and preventriculosis. In the present review the term cardiospasm will be used for the sake of simplicity and uniformity.

Since this term has been used rather loosely, even to include those patients with symptoms but without objective findings,[6] it may be well to make clear exactly what is meant by and included in the syndrome. Cardiospasm is the term used to include those patients who show dilatation and hypertrophy of the esophagus, together with a cardiac orifice which, at postmortem examination, is of normal size and without organic obstruction.[49] At postmortem examination the orifice permits the passage of a finger with ease, and water introduced into the esophagus at that time will run through the unnarrowed orifice. In short, the cause of the obstruction is not active after death. In life,

diagnosis rests on the ability of the examiner to demonstrate non-organic obstruction at the cardiac sphincter.

First description of this disease has usually been accredited to Purton[38] in 1821. Recently it has been shown that it was described as far back as 1672, when Thomas Willis[51] reported a patient with the typical findings.

Etiology. Many possible explanations have been given for cardiospasm, particularly since the latter part of the 19th century. They fall naturally into two groups, those concerned with changes in the esophagus itself, and those accounting for the difficulty through the influence of adjacent organs and tissues. A great many of these are easily discarded because of striking incompatibilities with the physiologic and pathologic findings. For example, the dilatation present suggested that paralysis of the esophagus might underlie the changes. However, the hypertrophy of the walls, invariably present, surely indicates that activity is present, and indeed contractions may be seen with opaque media at roentgenoscopic examination. Lendrum[29] found in 13 cases no evidence of organic narrowing at the cardia, evidence against Mosher's theory of fibrosis of the terminal portion of the esophagus. Kinking was absent in all early cases with moderate dilatation, speaking against any prime importance of kinking as a mechanism of obstruction.

Extra-esophageal lesions as a cause of cardiospasm were suggested some 50 years ago when Handford,[18] in 1888, in reporting a patient showing cardiospasm together with hypertrophy of the heart and dilatation of the aorta, brought forward the possibility that compression between the aorta and the diaphragm was significant. This is obviously erroneous, but other theories related to extra-esophageal conditions have taken its place. All these will not be repeated here. At one time Mosher[32a] suggested from case studies that the passage of the esophagus past the surrounding liver tissue—the liver tunnel—might produce the clinical picture. Tissue studies have not confirmed this concept[29] and diseases producing hepatic enlargement do not obstruct the esophagus. Apparently Mosher has abandoned this theory, for his later reports[32b] suggest still other unconfirmed possibilities; such as fibrosis of the edges of the crura, peri-esophageal fibrosis in the crural canal, or fibrosis of the esophagus itself. Jackson[23a] has postulated that spasm of the diaphragmatic crura, or their failure to relax, compresses the esophagus, producing obstruction. Hill[19] also suggested a similar mechanism. He believed that no actual spasm of the crura occurred, but that incoördination took place in relaxation to let food through. The observation[53] of obstruction both above and below the diaphragm appears to rule out the possibility of phrenospasm as a cause of the clinical picture.

The term cardiospasm arose from the concept of von Mikulicz in the 19th century that the cardiac sphincter was in spasm. Despite difficulties in the demonstration of a true anatomic sphincter, this view has persisted up to the present time. As early as 1888 Einhorn[10] suggested another possibility concerning the cardiac sphincter. He described a patient in whom he could pass the stomach tube without resistance and concluded that the cardia probably failed to open reflexly during the act of swallowing. Kronecker and Meltzer[26a] had shown that nor-

mally the cardia easily opens with each act of swallowing. So the theory of the failure of the cardia to relax, or achalasia, had its beginnings. Again, in 1896, Rolleston made the same suggestion independently,[21] but it was not until the work of Hurst, 1913, that the theory received attention. Hurst introduced the term achalasia.

Early observations by Hurst[21] indicate that food normally travels down the esophagus, forced forward by a peristaltic wave. On reaching the cardia it pauses for a short while and then enters the stomach, apparently through active relaxation of the last inch or more of the esophagus, which acts as a functional sphincter. This sphincter receives a dual nerve supply, through the vagus nerve to Auerbach's plexuses and through the sympathetic nerve supply. It has been reported that no such supply exists,[5,17,35] and that definite responses occur.[27,47] The latter view appears to be acceptable.

If one accepts the above innervation of the cardiac sphincter, it has been pointed out[21] that four possible conditions suggest themselves as affecting the cardiac sphincter abnormally. 1, Overactive vagal influences would produce a patulous sphincter and a tonic esophagus. 2, Underactivity of the vagus would result in a lack of inhibition, so that, although not in spasm, the sphincter would fail to open for a bolus of food. This condition would be achalasia and no hypertrophy of the sphincter would be expected. Hypertrophy is found but rarely, and the inclusion of such cases is doubtful, as will be evident from remarks under "Diagnosis." 3, Sympathetic stimulation would cause true spasm of the sphincter; and 4, paralysis of the sympathetic fibers would permit unopposed vagus activity.

The authors point out that organic lesions would be responsible for the second and fourth conditions, while a nervous reflex would be more likely to account for the first and third. They further think it doubtful that cardiospasm ever occurs as a purely functional disorder in so-called nervous people, for in their experience hysterical dysphagia is due to a disturbance of a neuromuscular control of the voluntary part of the act of deglutition involving the upper esophagus and not the cardiac sphincter. Intermittency and not permanency of change would be expected with sympathetic stimulation.

Results of nerve section in animals have tended to confirm the above views. As far back as 1839[40] it was known that vagal section in rabbits caused stasis of food in the esophagus. Kronecker and Meltzer[26b] and others have shown similar results. More recently Knight[25a] has investigated the subject. He found that the type of response obtained from electrical stimulation of the extrinsic nerves to the thoracic esophagus appeared to depend on the nature of the muscle content. Results obtained from the lower portions of the esophagus showed the presence of an intrinsic sphincter mechanism with relaxation on vagal stimulation and contraction on sympathetic stimulation. Excision studies on nerves confirmed these findings and bilateral division of the vagi resulted in the clinical symptoms and Roentgen ray appearances of achalasia, the effect being permanent and increasing in severity as time went on. Subsequent sympathetic denervation of the cardia resulted in a complete cessation of symptoms and Roentgen ray evidence that food then entered the stomach. It was thus shown that the esophagus gets

a sympathetic innervation, and that there is a true cardiac sphincter. Section of these nerves confirmed Hurst's opinions on the human. Ferguson[14] obtained similar results on monkeys following vagotomy, with achalasia of the cardia.

From such studies, lesions of the vagus might be expected in patients. Patients are on record with vagal lesions[37] but in Lendrum's series 10 of 13 cases with adequate sections showed entirely normal vagus nerves. In 1924 Hurst suggested lesions of Auerbach's plexus and subsequently Rake[39] demonstrated such changes, with enlargement of the ganglia, cellular infiltration and later fibrosis, with scar formation and replacement and disappearance of the ganglion cells. All 11 cases up to the report of 1930[21] showed these changes. Some[4,29,33] have confirmed these findings while others[15a] have not. Lesions, of course, may be elsewhere in the vagus. Lendrum found in every one of his patients a striking or complete absence of ganglion cells in the plexus and demonstrated that the loss was equally great in the undistended portion of the lower esophagus, a factor against these changes being merely secondary to pressure.

Several causes, such as spread of inflammation from the esophageal lumen, syphilis, infective ganglionitis, primary vascular disease, congenital abiotrophy, and others have been suggested[21] but none has been accepted and the cause remains unknown. Furthermore, other bilateral lesions of the vagus, as already stated, could give rise to the same clinical picture. The disease has not escaped attempts to relate it to vitamin deficiency, for Etzel[13] has demonstrated destruction of the ganglia in vitamin B_1 deficiency. One would suspect, however, that vitamin B_1 deficiency would more likely be secondary than primary.

There is, therefore, considerable evidence to substantiate Hurst's views that a failure of the sphincter to relax is the cause of the esophageal retention. Reports on work with the weighted mercury bougie support this contention. Hurst found that such a tube may be dropped into the stomach through the esophagus in a patient with this clinical picture without resistance. If obstruction were due to spasm, resistance would be anticipated. At times he has found a tight gripping of the tube both on introduction and withdrawal, indicating actual spasm. This spasm has disappeared, however, with treatment of the esophagitis and has been ascribed to it.

The ease of inserting an instrument into the stomach with little evidence of spasm has been confirmed by some[44,53] and denied by others. Walton[49] states that a bougie passes the opening with great difficulty and is gripped firmly so that considerable force is required to withdraw it. There is, however, no hypertrophy of the sphincter as one might expect with spasm. The fact that two such authorities as Hurst and Walton disagree on such an important and apparently easily demonstrable point leaves one at a loss whether to accept the concept of spasm or of achalasia. Knight[25c] suggests that there may be two types of disease, one due to spasm, the other to achalasia. The Reviewer feels, however, that although this may be true it is quite strange that only patients with achalasia should seek out Hurst, and only those with spasm, Walton.

Pathology. Studies on the pathology of cardiospasm are few, due to the fact that the condition is uncommon and the treatment is effective. No attempt will be made to cover extensively the pathologic features. Early in the disease peristalsis presumably overcomes the resistance of the sphincter and prevents the development of symptoms.[21] When hypertrophy of the esophageal wall becomes inadequate to overcome this resistance, dilatation, accentuated by vagal paralysis, results. Peristaltic waves then would be ineffective, for they would not close the esophageal lumen to move the contents along. They would, however, cause further hypertrophy of the muscle. Food would accumulate in the esophagus until the column of food were sufficiently heavy to open the sphincter by gravity. Hurst's studies indicate that a column of food approximately 8 inches high is necessary. He states that when food is taken, nothing passes into the stomach at this stage until the contents of the esophagus are about 8 inches high, and then with further ingestion of food or fluid, the esophageal contents pass into the stomach until the food column is again 8 inches high, when the sphincter closes.

The marked dilatation of the esophagus has been described[28] as taking on three general forms—fusiform, which is the most common, flask-shaped, and sigmoid-shaped—the last probably being the terminal stage due to lengthening as well as dilatation of the esophagus. It is the rarest type. Dilatation becomes more marked than in any of the organic obstructions, due, at least in part, the adherents to the vagal paralysis theory believe, to reduced vagal tone. Hypertrophy has already been mentioned. Esophagitis is usual in the advanced stages of the disease when stagnation of food is constantly present. It, and ulceration, are considered secondary phenomena. Diverticula may form, and malignant degeneration sometimes occurs.[24] Hurst has found an associated hypertrophy of the salivary glands, especially the submaxillary, and this finding may be observed clinically. At postmortem the glands are normal except for their size, which probably results from overactivity.

Hypertrophy and dilatation end approximately an inch above the cardiac end of the esophagus. This terminal portion, the sphincter, is normal in size.

Other changes, such as those in Auerbach's plexus, have already been noted under "Etiology."

Clinical Picture. The disease may be well established before any symptoms develop. This has already been discussed, and is due, no doubt, to the ability of the esophageal musculature to overcome the obstruction. When hypertrophy fails to clear the esophagus, food accumulates and symptoms develop. At any rate, patients who have had very minimal dyspepsia[53] have come to autopsy with enormous thickening and dilatation of the esophagus in old age. Symptoms are not necessarily delayed, however, for the disease has been described in children in the first few days of life.[2]

The age of onset of symptoms varies widely, from infancy to extreme old age, but the disease is one usually of young adults. The average age has been reported as from 30 to over 50 years. In Walton's group, the average age when first seen was 52½ years. MacMillan[30] found the greatest incidence between 30 and 40. Lambert[28] gives the average

age as 40. Both males and females have been reported as being more frequently afflicted.[46] The disease is known to have lasted over 40 years.

The typical findings of cardiospasm need not be recapitulated here. There are three common important symptoms—difficulty in swallowing, regurgitation of food, and pain. Food seems to stop before entering the stomach. It seems to stick beneath the lower sternum. At first the dysphagia may occur only under emotional stress or with rapid eating, and may then be intermittent with periods of relief for day or weeks. Cold liquids are described as giving as much difficulty as solid foods. Warm liquids are swallowed more easily, but at times there are exceptions to this rule.[46] Solid foods sometimes are swallowed more easily than liquids.[49]

Difficulty in swallowing may not be very obvious. It may be accompanied by substernal pain which may be mild or extremely severe. If marked, as it is in about 25% of the patients, it may overshadow difficulty in swallowing and lead to erroneous diagnoses, such as gallbladder colic.

Pain of anginal type has been known to accompany cardiospasm. Verbrycke[48] reported 23 patients with some degree of aortitis, aneurysm, or angina, but a common etiology has not been brought to light. Attacks of pain on swallowing in patients with evidence of coronary disease and spasm of the cardia have been very similar to those of the angina of effort.[9] Dyspnea and attacks of suffocation are not unusual in the advanced stages.

At first regurgitation may be absent. Later the patient may regurgitate even before leaving the table. There is no nausea and the material raised is alkaline in reaction, and contains undigested food and mucus. This is not vomitus in the true sense for it does not come from the stomach. Eventually, as Walton points out,[49] regurgitation may occur spontaneously, or may be induced by taking a deep breath, by voluntary retching, or by tickling the fauces. It may then occur at varying periods following the meal, even during sleep, and may stain the patient's pillow or awaken him by regurgitation into the nose. Such a series of events has led to aspiration of food into the trachea and to the development of lung abscess.[41]

After the cardiospasm is well established, distress following meals, especially with fulness and discomfort, is common, and the patient may learn to regurgitate when the distress bothers him. Wasting may be extreme. The history may, therefore, simulate that of carcinoma of the stomach. Loss of weight is usually present and often reaches a certain level at which it remains constant.[11] Thus, symptoms may be atypical, and, in the absence of dysphagia in the history,[23b] the esophagus may not be suspected as the site of the lesion. Patients may have the impression of swallowing all right and still complain of vomiting.

The mode of onset of the clinical picture varies. Symptoms certainly do not always occur in the first stages of the disease. Mild at first, they may gradually develop and suddenly give way to acute difficulty with solid foods. This has been ascribed to sudden decompensation of the esophageal musculature. Sudden onset of symptoms is unusual, but does occur.[12] Freeman[15b] says the onset is usually

sudden, but most observers describe a gradual development of distress, at first with coarse foods, and later with more refined articles of diet. Acute flare-up of symptoms may be related by patients to emotional causes, financial worries, and the like,[23b] and a psychogenic theory has been developed.[52]

Cardiospasm has been described in association with a number of diseases. Heart disease has already been mentioned. Others are bronchiectasis, asthma, peptic ulcer, and diverticula. Bronchiectasis, pneumonia, and lung abscess may result from overflow from the esophagus during sleep,[41] although cardiospasm is not generally recognized as a cause of lung abscess. Sampson believes that in cases of unexplained pulmonary suppuration the esophagus should be studied routinely, in spite of the absence of symptoms referable to it.

Diagnosis. As a rule, cardiospasm gives little trouble in diagnosis. The clinical picture is usually characteristic and leads to confirmation by Roentgen ray studies, which, as a rule, suffice to clarify the problem. The appearance of the lower portion of the barium-filled esophagus, with a smooth tapering occlusion, is characteristic, and contrasts with the irregular appearance produced by carcinoma. Most clinicians feel that the recognition of the usual Roentgen ray findings is sufficient. However, Jackson[23b] believes that esophagoscopy is essential to confirm the Roentgen picture, for he has found carcinoma in patients reported by Roentgen ray examination as having cardiospasm. Freeman[15b] takes the usual point of view that, as a rule, Roentgen ray studies are adequate, but he believes there is a small group in which esophagoscopy is necessary.

Spasm of the cardia has been ascribed reflexly to carcinoma and ulcer of the stomach. It is also known that congenital pyloric stenosis may be accompanied by hypertrophy and dilatation extending above into the esophagus.[22] It is evident that, in the diagnosis of cardiospasm, disease below the cardiac sphincter must be ruled out.

Hysteria must be differentiated in young women. It tends to disappear as years go on. Cardiospasm does not.[49] The characteristic Roentgen ray picture is absent in hysteria. Other causes of dysphagia must also be considered. Walton states that he has seen esophageal dilatation comparable to that of cardiospasm in obstruction due to mediastinal tumor, but the obstruction was not at the diaphragmatic level. This degree of dilatation in organic obstruction is contrary to usual statements.

One condition which closely simulates cardiospasm is muscular hypertrophy of the cardiac sphincter, comparable to the pylorus in congenital hypertrophic pyloric stenosis. This disease is very rare, and the Roentgen features and symptoms may simulate closely those of cardiospasm. Obstruction persists after death.[25c]

In general, the differential diagnosis includes carcinoma and stricture of the cardia, congenital narrowing of the lower end of the esophagus, congenital hypertrophy of the cardia, para-esophageal hernia, esophageal diverticulum, angina pectoris, and the other disease states already enumerated.

Treatment. Drugs have been of no use. The most successful measure has been some form of dilatation of the cardiac end of the esophagus.

Since an ordinary bougie may be deflected from the cardiac orifice with danger of perforation, special procedures and bougies have been devised and have become standard forms of treatment. These include Hurst's mercury-weighted tube, hydrostatic dilators, use of the esophagoscope and a bougie, and digital dilatation through an opening in the stomach. All aim at an overdistention of the cardia to relieve the obstruction through injury to the circular muscle. Most popular are the methods of Hurst[21] and of Plummer,[31,36] the latter at times being modified to use air in place of water.[15b]

Details need not be given here. Plummer's method consists of the passage of a hydrostatic bag over a silk thread which has been slowly swallowed into the intestine until it may be held taut to guide the bag into the cardiac orifice. Then, hydrostatic dilatation of the silk covered bag is carried out. Until January, 1932, 810 patients with cardiospasm were observed at the Mayo Clinic.[31] Of these, 804 were dilated, and of 670 traced, 475 were considered cured, 105 moderately relieved, and 32 slightly relieved. Nine died of splitting of the esophagus. Thus, 71% of those receiving dilatation received complete relief. In most instances only one dilatation was required, but as high as 10 were given to some patients. This method has given good results in the hands of others as well,[34,44] and at times symptoms have been relieved without any appreciable change in the Roentgen appearance of the cardiac orifice.

Hurst's method utilizes a mercury weighted bougie. It is a flexible rubber tube filled with mercury to a sufficient weight to find its way through the cardiac orifice. It is first passed under fluoroscopic control in increasingly larger diameters (28 to 34 gauge) and, in Hurst's experience, has found little resistance. Patients then pass the largest tube themselves before meals, and leave it in place for 5 minutes. As symptoms warrant, the time and frequency of passage is reduced until it is passed in the morning only, then on alternate days, and finally once a week until discontinued altogether. Treatment is also directed toward the esophagitis. The patient is instructed to eat slowly, chew thoroughly, eat 4 meals a day, omit irritants from the diet, and to finish the meal with water or milk to wash the food into the stomach. The esophagus is emptied either voluntarily or by lavage after meals until the evidences of esophagitis have disappeared. All have not obtained the good results reported by Hurst,[49] and some have found in certain cases difficulty in passing the sphincter.[25c]

Artificial hyperpyrexia[52] and local diathermy[3] have been advocated. Generally, dilatation gives good results, but in certain instances fails. In these patients operative procedures have been used. These include plastic repair of the esophagus or stomach, and short circuiting procedures. One of the first operations was that of Mikulicz, which consisted of opening the stomach and dilatation of the cardia from below. Most procedures, however, are directed to eliminate the obstruction of the cardia. Their variety reflects in part the number of concepts of the cause of this condition. Gastrostomy alone is only palliative. Other procedures include an operation analogous to the Rammstedt procedure for pyloric stenosis. Other types of cardioplasty are designed to destroy the circular muscle and leave a large permanent opening. Invagination

of the esophagus, division of the vagi, and anastomoses between the esophagus and stomach have been tried. Certain degrees of success have been ascribed to practically all of these procedures.[11,16,21,28,46,49,53] Division of the vagi has aggravated the symptoms.

From the work of Knight[25a,b] one might expect that sympathetic denervation would be beneficial, and this has been true in some hands.[1,7,11,45] Craig and his associates first injected the ganglia with procaine and obtained relief before they attempted the operation. DeBakey[8] has carried out the same procedure with striking relief of symptoms and Roentgen ray evidence of passage of food without difficulty into the stomach. However, at short periods following actual section of the nerves, symptoms and signs of obstruction at the cardia returned.

WILLIAM A. SODEMAN, M.D.

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PEDIATRICS

UNDER THE CHARGE OF
ALVIN E. SIEGEL, M.D.
MACON, GEORGIA

THE USE OF SULPHANILAMIDE AND SULPHAPYRIDINE IN CHILDREN.

THE first drug of this group that was used as a therapeutic agent was prontosil. Domagk, who has been awarded the 1939 Nobel prize for this work, in 1935, observed the protective action of prontosil, a synthetic azo dye, on artificially produced streptococcic infection in mice. Similar results were also noted with a related compound which had the additional advantage of being more soluble. This became known as "prontosil soluble." Favorable observations were made on the action of these drugs in man, and they became the object of intensive study and research in Germany, France, England and the United States. The early interest in the drug was centered on its action against streptococcic infection. This organism has such great morbidity and mortality rates that an agent which would combat successfully the various manifestations of streptococcic infection is of the greatest importance. As soon as the drug was available commercially its use became widespread and often injudicious, so that along with reports of great benefit there began to appear mention of untoward and harmful results in its use. The early reports of its usefulness in streptococcic infection have, however, been justified and its use has spread to the treatment of other forms of infection.

According to Johnson,[23] some very interesting facts were brought out concerning the mode of action of these compounds. In the test tube or in contact with culture media containing viable organisms of known potency, the drug showed no bactericidal and only mild bacteriostatic activity. On the other hand, in the animal body the same organisms soon disappeared from the body fluids after administration of the drug. It was suggested that the curative action of the drug was due to a stimulation of the natural defenses of the body to such an extent that they were able to overcome the infection. Later it was shown that prontosil was reduced in the body with the formation of a compound which is known chemically as para-aminobenzenesulphonamide. This compound was given the non-proprietary name of sulphanilamide. It showed, but to a lesser degree than prontosil, the peculiar discrepancy between its *in vivo* and its *in vitro* effects.

The first applications of prontosil and of sulphanilamide were in the treatment of beta hemolytic streptococcal infections. Knowledge of its striking effect was especially impressed upon the public mind by the newspaper and radio stories of the beneficial effects of the drug in the severe streptococcic throat infection that threatened the life of a son of the President of the United States. Soon it was being used widely for streptococcic sore throat and other forms of streptococcic

infection. Hoyne and Bailey[22] gave an unfavorable report of its use in the treatment of streptococcic carriers. They found that, on the basis of the results observed by them, whatever value it may have in the treatment of acute streptococcic infections, it was not effective in the eradication of hemolytic streptococci from the noses and throats of scarlet fever patients at the end of a 4-week quarantine period.

Hickey[16] stated that in no branch of medicine had the effect of this new form of therapy been more effective than that in otolaryngology. This included such diseases as pharyngitis, nasopharyngitis, tonsillitis, peritonsillar abscess, cervical adenitis, otitis media, mastoiditis, otitic sepsis, streptococcic meningitis, ethmoiditis, orbital abscess and erysipelas. McLaurin[30] stated that the otolaryngologist would find that he could use sulphanilamide to advantage in treating patients suffering with the following conditions: 1, Pharyngitis, especially of the ulcerative streptococcal type; 2, sinusitis with purulent or seropurulent discharge; 3, rhinitis associated with a pharyngitis or sinusitis; 4, otitis media complicating a nasopharyngitis; 5, mastoiditis and cellulitis about mastoid wounds, especially when due to beta hemolytic streptococci; 6, purulent conjunctivitis associated with upper respiratory infections; 7, laryngitis or tracheobronchitis associated with an active pharyngitis; 8, Ludwig's angina; 9, furunculosis of the outer ear canal; 10, acute cellulitis with or without furuncle formation of the upper lip, columella, wings of the nose or floor of the nose, and 11, cavernous sinus thrombosis. Complications such as pneumonia of certain types and meningitis of otogenic origin or the result of sinus infections, formerly almost uniformly fatal, also responded to the use of the drug. He pointed out also the very important observation that children suffering from the acute infections enumerated seem to respond even more promptly to sulphanilamide than do adults, and they do not seem to be so definitely disturbed by the toxic effects of the drug.

Maybaum, Snyder and Coleman[33] were opposed to the indiscriminate administration of sulphanilamide for infections of the upper respiratory tract, many of which run a self-limited course. They claimed that the free use of the drug, aside from the dangers of toxicity, frequently obscures the clinical picture and often gave rise to a latent course of the disease. They felt that it was inadvisable to give the drug during the period of observation of a patient for a suspected mastoiditis, sinus thrombosis, petrositis and similar conditions because of the risk of masking the clinical picture and thus interfering with the diagnosis and surgical indications. In the same way Converse[11] remarked that the extraordinary success of sulphanilamide in the treatment of streptococcic otogenic meningitis had led to the widespread use of the drug in all cases of otitic infection in which the beta hemolytic streptococcus could be identified. While such enthusiasm for specific chemotherapy could be understood, he felt that the practice was open to criticism. He pointed out that the patient with meningitis was under hospital observation, and that treatment was continued until the spinal fluid had returned to normal. On the other hand, the patient with acute otitis media or mastoiditis received sulphanilamide only as long as there was persistent pain or discharge, and treatment was usually stopped on clinical instead of on laboratory evidence. Inadequate

sulphanilamide therapy has been followed by recurrence of otitic infections with beta hemolytic streptococci. The absence of the organisms should be proved by laboratory observations. The use of sulphanilamide in streptococcic ear diseases should be reserved for the treatment of infections that threaten life and it should not be used for the treatment of infections of minor severity. Inadequate treatment will result in recurrences and further spread of the infection. Hospitalization of patients receiving the drug is required not only because of the necessity of close laboratory observation, but because the amount of sulphanilamide required usually is so large that the danger of toxic manifestations demand close clinical observation. Woodward[45] agreed with the general opinion that sulphanilamide is particularly valuable in hemolytic streptococcic and certain types of pneumococcic infection. Since the majority of acute ear infections are due to these organisms, its routine use does affect the incidence of acute otitis media, the percentage ratio of operations to otitis media, the complications and results of treatment of acute ear infection.

Streptococcic meningitis is closely related to streptococcic otitis disease, and in fact it is often a consequence of the latter. Retan[35] observed that the advent of sulphanilamide had revolutionized the treatment of meningitis caused by *Streptococcus hemolyticus beta.* Formerly the disease had a mortality rate of 97% but under the use of this drug it had been reduced to 20%. Toomey and Kimball[42] felt that sulphanilamide was the therapy of choice in treating patients with beta hemolytic streptococcus meningitis, but they emphasized the importance of draining any localized area of infection by proper surgical procedures. They did not find it necessary to adopt the method of forcing fluids to produce increased perivascular spinal drainage in treating their patients. This is a hospital procedure and not easy to carry out in private practice. It was possible to secure a good concentration of the drug in the spinal fluid by simple ingestion. They first administer a massive initial dose of the drug followed at once by frequent maintaining doses. Along with this any focus of infection is removed surgically as soon as possible. They leave the hydrostatics of the spinal fluid alone unless the pressure is extremely high. As a result of this régime they found that, although sulphanilamide may prolong the life of a patient ill with a streptococcic meningitis, it would not give a complete cure if there was an untreated focus of infection. It will often immobilize the infection while the focus of infection is being localized.

Tixier[41] employed sulphanilamide with good success in the treatment of cerebrospinal meningitis of various origins. He found that the oral route of administration was the best under most conditions. The intraspinal administration may be necessary in extremely severe cases. He also used the drug as a preventive in epidemics of cerebrospinal meningitis by giving the drug to persons exposed to the infection.

According to Bucy[9] through an error in diagnosis a right cerebellar abscess was exposed with a bilateral suboccipital craniectomy. The contents of the abscess were aspirated and the surface of the cerebellum was contaminated with pus swarming with hemolytic streptococci, thus exposing the ventricular system and the subarachnoid space to this

infection. The abscess was not drained but the administration of sulphanilamide was begun at once. The patient improved steadily with almost no febrile reaction. At no time were there any signs of meningitis or of refilling of the abscess. This case suggested that all brain abscesses should be treated by trephining over the abscess, aspirating the pus and administering sulphanilamide. This conservative treatment might be all that was required, but if it did not clear the condition, radical treatment by drainage of the abscess could easily be done.

Another organism that has responded well to treatment with sulphanilamide is the gonococcus. Adler[1] used sulphanilamide in the treatment of 22 cases of gonorrheal vaginitis, 5 cases of gonorrheal urethritis in boys and 9 cases of gonorrheal conjunctivitis. In the latter, it was shown that the results are better with sulphanilamide than with any other form of treatment. In the boys' urethritis, 4 of the 5 cases gave prompt and definite response to the sulphanilamide therapy with cessation of discharge and with negative smears after an average of 2 days of treatment.

In an outbreak of gonorrheal ophthalmia in a home for infants and very young children, Newman[34] found that while improvement followed the use of local germicidal agents such as argyrol there was a marked tendency to relapse and the appearance of new cases in the contacts. Prompt improvement followed the initiation of sulphanilamide therapy with permanent disappearance of discharge and negative smears in 4 or 5 days.

Hoberg and Reck[18] studied the effect of sulphanilamide treatment of gonorrheal infections in 50 children. In their opinion sulphanilamide is justified in the treatment of gonorrheal infections in children. One advantage is its ease of administration without the psychic trauma that often results with irrigation treatments. In contradistinction to this, Holmes, Jones and Gildersleeve[21] reported that in 42 patients with gonorrheal vulvovaginitis treated with sulphanilamide by oral administration, 16 were relieved to the point of being able to return to school, having satisfied the Board of Health requirements of having three consecutive negative smears without vaginal discharge. Of these 16, 8 had recurrences of either positive smear or discharge in from 2 to 6 weeks. The failures did not seem to be due to inadequate dosage as the cases with high sulphanilamide blood serum concentrations showed as frequent failures as those with low levels of sulphanilamide. These discrepancies of results are difficult to explain. However, it may be that the important factor in permanent cure is not so much the high concentration of sulphanilamide in the blood at the beginning of treatment as it is the maintenance of an adequate dose for a period of time to insure complete eradication of the infection.

The use of sulphanilamide has become very popular in the treatment of urinary infections. One of the early advocates of this use of the drug was Helmholz.[14a] In discussing the applicability of the various urinary antiseptics he stressed the necessity of the treatment being useful to any patient in any stage of the disease. He pointed out that methenamine in subacute and chronic infections of individuals whose urinary passages are normal is a very satisfactory drug, but that it

is of little use for patients who have acute infections, urinary stasis, or reduced renal function. This also applies to the ketogenic diet and mandelic acid, each of which is dependent for its action on a certain degree of acidity of the urine. With these latter two methods, it is necessary to control both the acidity and the concentration of the bactericidal substance. The use of sulphanilamide is much more simple. It can be given in the acute stage of the disease in addition to the usual forced intake of fluids and urinary alkalinization. Although it acts best in an alkaline urine it acts also in acid urine and can be used in any phase of the disease. It gives very excellent results by oral administration but where the necessity arises it can be administered in the intravenous form.

In another contribution, Helmholz[14b] emphasized that the diagnosis of urinary infection must include the type of infection, the state of urinary drainage and renal function as well as the presence of foci of infection in the urinary tract. Sulphanilamide has given the best results in the greatest number of conditions. In infections with *Strep. fæcalis*, sulphanilamide has not proved successful and in this condition mandelic acid gives better results when the necessary acidity and concentration of the drug can be obtained.

Summerfeldt and Mitchell[40] studied 40 cases of urinary tract infection in children under treatment with sulphanilamide. Only 1 child manifested an intolerance. This patient had a cyanosis after the smallest doses of the drug. Although it has been customary to restrict the amount of fluids in administering sulphanilamide in adults for the purpose of securing better concentration of the drug, fluid restriction in children is not advocated because of the ease with which dehydration and acidosis develop especially in infants. For this reason the dosage of sulphanilamide in children has to be relatively higher than the doses given adults. In their series the authors found that urinary infections responded well to sulphanilamide therapy. *B. coli* infections respond readily to this treatment but *Strep. fæcalis* infection is more resistant to this therapy.

Some success resulted from the treatment of pneumonia and pneumococcic infections with sulphanilamide. The results of treating this type of infection with the sulphanilamide derivative, sulphapyridine, have been so much more dramatic and successful that little space will be devoted to references of the use of sulphanilamide in pneumococcic infection. However, the results of any form of treatment in pneumococcic infection of the meninges have been so uniformly unsuccessful that record must be made of the fact that first with sulphanilamide some success against this type of infection was made. Hewell and Mitchell[15] reviewed the literature and found that 30 cases had been reported of recovery from pneumococcic meningitis. The treatment of these was in part the use of sulphanilamide or related compounds. They felt that it was reasonable to conclude that the sulphanilamide compounds were responsible for these recoveries in most instances, since the mortality was so high with other forms of treatment. Of the patients who received sulphanilamide and recovered, only 1 showed pneumococci in the blood culture. Negative blood cultures were reported in 16 patients and in 13 there were no blood cultures reported.

Of the 8 patients who received sulphanilamide and died, the blood cultures were positive for 7. This indicated that even with the use of sulphanilamide a blood stream infection with pneumococci is a factor in mortality and with such cases massive doses of sulphanilamide should be tried.

With such remarkable results following its use in a number of types of infection, it was only natural that the compound would be tried in many others, especially in those in which our treatment had been unsatisfactory. Experimental work by Kelson[24] on poliomyelitis in monkeys showed that there was no favorable reaction to the use of sulphanilamide in this disease. Hill and Goodwin[17] found that prontosil was effective in treating persons infected with *Plasmodium vivax* and with *Plasmodium falciparum*. This was especially true when the patients had had previous attacks. They remarked that the drug was more useful in the treatment of chronic and malignant infections and was not so useful in the treatment of benign and initial infections.

Of the 58 patients with rheumatic fever or chorea given sulphanilamide by Massell and Jones,[32] 31 (53%) showed toxic reactions. The chief manifestations were rash and fever. The rash was pink or red and usually maculopapular. It occurred on all parts of the body. There was slight, if any, itching associated with it. Occasionally the rectal temperature rose as high as 103° F. Fever frequently occurred unassociated with rash and then was usually higher than fever which accompanied rash. The toxic reactions occurred most frequently between the seventh and twelfth days after beginning the use of the drug. In 9 patients with toxic symptoms the repeated administration of the drug resulted in the development of a tolerance. Patients ill with rheumatic fever were particularly prone to the development of severe febrile reactions. This fact, together with the lack of any observed beneficial results, contraindicates the administration of sulphanilamide in the presence of acute rheumatic fever. The drug was given to 7 patients with slight to moderate chorea. In this condition there was no demonstrable improvement.

Anderson[3] treated 63 measles patients with sulphanilamide. At the same time a control group was under observation. It was found that the drug showed little effect in shortening the febrile period after admission to the hospital, but there was a slight reduction in the mean duration in the sulphanilamide-treated cases. The results did not suggest that this compound was of any great value in hastening the cure of the major complications of measles, but the duration of bronchopneumonia was materially shortened in the cases that had received sulphanilamide. Hogarth[20] found that routine administration of sulphanilamide by a fixed procedure of dosage gave a lower incidence of complications than those who did not receive such treatment. The results were not equally good with all complications, the incidence of enteritis being entirely unaffected by the drug. In regards to other complications, it would seem that there is some prophylactic value as the incidence of bronchopneumonia, otitis media and cervical adenitis was less than in the controls. The evidence showed that sulphanilamide was of value in reducing the incidence of complications due wholly or in part to secondary invasion by hemolytic streptococci, and the

best results were observed in pure streptococcic complications such as otitis media.

Wesselhoeft and Smith[43] found that sulphanilamide therapy in the eruptive stage of scarlet fever in the accepted dosage did not reduce the toxicity as manifested by intensity of the eruption nor the duration of the fever. The drug, given during the initial stage of the disease, did not reduce the incidence of complications. In cases in which the drug was continued longer the incidence was markedly decreased. It was not helpful in the complications involving the respiratory tract, but it was useful in certain infections of the mastoid cells. Infections of the blood stream and meningitis were found to be definite indications for the use of sulphanilamide. The carrier rate was not reduced by the use of the compound.

Stewart, Rourke and Allen[39] made a study on the excretion of sulphanilamide. They found that in man it was excreted almost entirely by the kidneys in either the free or in the conjugated form. The concentration of free and conjugated sulphanilamide in the blood resulting from a given per pound dosage was quite variable in different individuals; therefore it is important to have frequent determinations of blood level during intensive therapy with the drug. After sulphanilamide has been stopped the drug is rapidly eliminated from the body if renal function is normal and urine volume is adequate. It was found that the concentration of conjugated sulphanilamide in the blood was much lower than that of free sulphanilamide, but the rate of clearance of conjugated sulphanilamide was greater than that of free sulphanilamide. Because the precipitation of excreted sulphanilamide in urine at room temperature has been demonstrated, the possibility of stone formation in the urinary tract is emphasized if the urine volume should become too small during sulphanilamide therapy.

Stewart and Pratt[38] studied the effects of the drug on breast-fed babies as well as the excretion of the drug through the mothers' milk. Free sulphanilamide is excreted in human milk in concentrations closely corresponding to the values present in the blood stream. The concentration falls rapidly in the milk when oral administration is discontinued. It was found that breast-fed babies of full-time nursing mothers did show clinical evidence of toxic manifestations when the sulphanilamide was present in the breast milk in concentrations of 7 mg. per 100 cc. Traces of the drug were found in the blood of the baby and the urines of these babies contained amounts varying from 1 to 2.6 mg. per 100 cc. during a 24-hour period. However, a nursing baby cannot obtain an adequate therapeutic dose through the milk of a mother receiving an average clinical dose. Sulphanilamide has been found in the cord blood and in the amniotic fluid of women following the oral administration of 5 gr. of the drug every 4 hours throughout labor.

Following the widespread use of sulphanilamide many reports appeared giving toxic and untoward effects of the drug. Bigler and Werner[7] stated that cyanosis occurring during sulphanilamide administration has been reported frequently. It does not seem to depend on the age of the patient, the daily dosage or the length of time the drug is administered. The cyanosis usually disappears soon after the

withdrawal of the sulphanilamide, but it may not completely disappear for several days. It is questionable as to whether this manifestation is of any serious import. Changes in the blood picture are also seen after sulphanilamide administration. An example of this is the case of granulocytopenia reported by Alpert and Forbes.[2] The dosage in this case was comparatively small. Despite that a leukopenia with 100% lymphocytes developed, there was no complicating stomatitis and the patient recovered. Because the administration of nicotinic acid to patients suffering from pellagra or radiation sickness will ameliorate the symptoms and decrease or eliminate the excretion of abnormal porphyrin, McGinty, Lewis and Holtzclaw[28] studied the effects of this treatment on patients receiving sulphanilamide. The response of the patients to the additional administration of nicotinic acid was most gratifying. The unpleasant symptoms and the porphyrinuria were decreased. The most definite clinical change observed was a clearing of the mental apathy so often present with the ingestion of sulphanilamide.

Bigler and Haralambie[6] presented a very extensive review of the literature on sulphanilamide. Particular emphasis was laid on the range and limitation of application of the preparation and on what has been found to be the optimal dosage and mode of administration with the different diseases. Sulphanilamide has proved to be one of the most effective drugs in the treatment of certain diseases and they predicted many new derivatives and compounds of sulphanilamide. They defined the fields of usefulness of the drug and in their discussion of the toxicity and reactions of the drug they attempted to show not only its dangers but also its innocuousness when it is used intelligently.

McColl[27] remarked that the clinical success of sulphanilamide in infections with streptococci, gonococci and meningococci stimulated the search for new and related chemical compounds of therapeutic value. Of these numerous derivatives, 2-para-amino-benzene-sulphanilamide-pyridine has come forth as a valuable chemotherapeutic agent because of its effectiveness against pneumococci as well as the other organisms affected by sulphanilamide. Among the names which have been applied to this drug are sulphanilamidepyridine, sulphone-pyridine, pyrideine sulphanilamide compound, dagenan, M & B 693. The Council on Pharmacy and Chemistry finally named it "sulfapyridine." This is a slightly bitter powder which commercially is offered in tablets usually of 0.3 to 0.5 gm. McColl found it useful in pneumonia and also in a number of other infections, and it required a smaller dosage than did sulphanilamide. The toxic effects were less noticeable. Besides pneumonia he employed it in bronchopneumonia, osteomyelitis, meningitis, ruptured appendix, cellulitis of the hand and of the shoulder, impetigo neonatorum and epidermolysis bullosa.

According to McLeod,[31] nausea and vomiting are frequent accompaniments of the administration of sulphapyridine. These reactions are not related to the dosage of the drug or to the blood level. Since vomiting occurs in individuals to whom the drug has been administered parenterally, the effect would seem to be central, in addition to a possible local action on the stomach. Morbilliform skin rashes have been reported as well as numbness and tingling of the extremities.

Cyanosis due to methemoglobinemia occurs, particularly if high blood levels of the drug are attained. More serious toxic manifestations may appear involving the hemopoietic system and the urinary tract. Although there have been numerous reports of acute hemolytic anemia in patients receiving sulphanilamide, there has been little information available concerning blood destruction in patients receiving sulphapyridine. Hemolysis, when present, is due to the sulphapyridine itself and not to the pathologic process such as a pneumonia. Granulocytopenia also occurs with sulphapyridine.

Somers[37] treated 143 cases of cerebrospinal meningitis with sulphapyridine. These cases were all treated under adverse conditions in grass shelters with insufficient and unskilled nurses and the crudest care and food. The clinical condition of the patient and the cerebrospinal fluid were the criteria for the dosage of sulphapyridine injected. The youngest patients usually received proportionately the largest doses as they were the most seriously ill patients. Infants tolerated injections of 0.25 gm. in 40 cc. of distilled water intraperitoneally and 0.5 gm. intramuscularly. Saline suspensions were later used instead of the distilled water and resulted in less pain. In those receiving larger doses herpes of the lips were often observed. More rapid general improvement followed the intraperitoneal injections than the intramuscular injections. In most of the cases the cerebrospinal fluid became clear before the temperature fell to normal. Arthritis of the large joints and stiffness of the neck usually persisted for some days after the general condition had improved. While the usual case mortality of this disease in the Sudan is from 68 to 80%, in the 143 cases observed in this report under treatment with sulphapyridine the case mortality was 10%.

Hamilton and Neff[13] reported a case of influenzal meningitis, with the same organism in blood culture, that was treated with sulphapyridine. Under this drug the patient recovered simultaneously from the clinical and laboratory standpoint. The patient became afebrile on the sixteenth day.

According to Banks,[4] acute hemolytic streptococcal peritonitis, in which no focus in the abdominal cavity is demonstrable, is a rare and very fatal condition. The disease is essentially the same whether associated with scarlet fever or not, being probably always preceded by hemolytic streptococcic septicemia. The entire treatment of acute primary peritonitis has been revolutionized by the introduction of the new drugs. Both sulphanilamide and sulphapyridine have such potent action on hemolytic streptococci in the blood stream, in the meninges and as this case suggests in the peritoneum, that it may be thought justifiable and even desirable to refrain from laparotomy in view of the risks in desperately ill patients. Where there is a demonstrable primary focus in the abdomen this does not apply. In the case reported the child had scarlet fever plus a peritonitis and recovered under chemotherapy administration alone.

Brown[8] treated 27 cases of gonococcal vulvovaginitis with sulphapyridine, 31 with sulphanilamide and 6 with the sulphanilamide compound called uleron. All the patients treated were from 3 to 10 years of age. The duration of the period of treatment was cut down to only 4 days for the girls receiving sulphapyridine and to 10 days for those receiving

sulphanilamide. Perhaps the chief advantage found for sulphapyridine was that there was no necessity for local treatment except for merely swabbing the vulva with 1 part of acriflavine in 1000 parts of glycerin for the first few days. Improvement is apparent within a few hours in some cases treated with sulphapyridine and always within a few days with both sulphapyridine and sulphanilamide. The greater majority of the cases when once cleared remained clear even many months later.

While sulphapyridine has been used in these and other forms of infection, its action against pneumococcic infections have been particularly striking. Of pneumococcal meningitis Cable[10] said that it is rare, having been noted 39 times in 36,848 cases admitted to the Dudley Road Hospital in the past 3 years. The rarity of the condition is offset by its fatality rate, which has been usually accepted as 100%. His case was the first successful case reported in which sulphapyridine was used. Dunlop and Laurie[12] reported another successful result with the administration of sulphapyridine. Yule[46] reported a case that recovered under treatment with this drug. Pneumococcic meningitis followed mastoidectomy. McKeith and Oppenheimer[29] reported 5 consecutive recoveries under treatment with sulphapyridine, of which 2 recovered. This was a very great improvement in the mortality rate.

Discussing the treatment of pneumonia in children with type-specific horse and rabbit sera, Hodes *et al.*[19] stated that the results have been good and in some instances striking. However, this form of therapy has certain disadvantages when used in children because the type of pneumococcus must be determined before serum can be started and difficulties in typing may cause serious delay in starting therapy. In addition to this objection sometimes more than one type of pneumococcus is found in a patient and it is impossible to be certain which organism is causing the pneumonia. As a further objection serious serum reactions, while infrequent, do occur occasionally in spite of all precautions. Many of the patients are too young to be coöperative and are greatly disturbed by serum administration. The cost of the treatments is another important consideration. Although the mortality rate for pneumonia in children is very low, the condition is sufficiently serious to justify search for an effective therapeutic agent. The authors found that sulphapyridine was effective in primary pneumonia and also in the pneumonia accompanying measles and pertussis. As a rule, the administration of sulphapyridine was followed within 48 hours by a fall in temperature to normal and by prompt improvement and in 71 cases they had no deaths. They called attention to the possible ill-effects following the use of this drug such as hematuria, granulocytopenia and anemia. They emphasized the necessity of leukocyte counts, hemoglobin determinations and urine examinations at least every other day on all patients receiving the drug so that detection of the development of these untoward effects can be made as early as possible. Because these ill-effects are only temporary so far as is known, the withdrawal of the drug or reduction of the dosage is important.

Wilson *et al.*[44] attempted to determine the value of sulphapyridine in the treatment of pneumonia in infants and children, making no distinction between croupous pneumonia and bronchopneumonia. A control group was studied in parallel to the sulphapyridine group, observing such factors as age, severity of the pneumonia, the time at

which there was clinical improvement, significant fall in the temperature and clinical recovery. The case fatality rate is so low in pneumonia in children that this cannot be taken as a criterion of the efficacy of treatment. In their control and sulphapyridine groups there was no fatality. In all 70 cases with pneumonia were studied, half serving as a control group and half receiving sulphapyridine. The characteristics of the disease in the two groups were suitable for comparison of the results obtained. The administration of sulphanilamide apparently shortened the course of the pneumonia by approximately 3 or 4 days. By a statistical analysis it was demonstrated that the fall in temperature and the clinical recovery were significantly earlier in the sulphapyridine group than in the control group. As far as complications were concerned the number of cases under observation was too small to allow of evaluating the effect of sulphapyridine in this respect. The optimum dosage could not be determined but these observations indicated that a dosage which secures a level of free sulphapyridine in the blood of approximately 4 mg. per 100 cc. is therapeutically active. It was found that there were wide individual variations in the levels of free sulphapyridine so that frequent estimation of the blood concentrations are necessary. Vomiting and cyanosis were present in about half of the patients receiving sulphapyridine. In no instance was the cyanosis sufficient to cause concern. In the control group a number of the patients manifested cyanosis and vomiting in the acute stage of their pneumonia. Two patients on the drug had cutaneous eruptions but none of the severer reactions of the drug were observed.

Barnett *et al.*[5] studied the clinical results of sulphapyridine in 23 infants and children. In this group, 14 had pneumonia, 3 had empyema, 4 bronchitis, 3 pneumococcic peritonitis, 1 influenzal meningitis and 1 subacute bacterial endocarditis. They had results confirmatory of the reports concerning the use of the drug in adults. They suggested that in pneumonia if definite improvement did not result in 24 to 36 hours specific serum therapy should be used if the clinical conditions indicated its use and if the material was available. The toxic symptoms that were encountered following the use of this drug were mild nausea, vomiting and slight mental confusion, all of which usually subsided even with the continued administration of the drug. None of these manifestations were ever of sufficient severity to interfere with the use of the drug. Cyanosis due to the accumulation of methemoglobin was seen in most of the extensively treated cases but was readily controlled by the use of methylene blue.

Reynolds and Slobody[36] concluded that sulphapyridine when properly used in the treatment of the pneumonias of childhood brings about a precipitous fall in temperature, followed by a rapid disappearance of toxicity and a return of the respiratory rate and general condition to normal. They found that the signs of consolidation may persist for the usual length of time, but convalescence is markedly shortened and complications are rare. They commented on the relatively large doses of sulphapyridine required by children. This was directly proportional to the lack of age in the patients as infants under 2 years of age required a further 50% increase in the size of the dose on the basis of body weight to bring about results comparable with those obtained in older children.

Litter, Litvak and Givan,[26] discussing the use of sulphapyridine in the treatment of pneumonia complicating pertussis, pointed out that vomiting, which is a predominating symptom of whooping cough, complicates the adequate administration of the drug. They found that the simple expedient of incorporating the drug in palatable vehicles was very useful. Sulphapyridine can be added not only to milk or fruit juices, but also to chocolate or malted milk. In addition, desserts such as mashed banana and cream, chocolate or rice pudding; and tapioca may be used. It has been found advantageous to vary the vehicle of administration. If emesis is at all prominent it is not possible to determine the amount of sulphapyridine actually ingested. In such cases the concentration of the drug in the blood must be observed by frequent blood studies necessitating frequent venipunctures. For several reasons this is not desirable, but especially in anemic and debilitated children. For this reason the authors have recommended rectal administration of sulphapyridine where pernicious vomiting interferes with the plan of dosage. They stress the need of larger doses than those given by mouth as the absorptive power of the rectum is less active.

Leopold and Sobel[25] treated 58 cases of lobar and bronchopneumonia in infants and children with sulphanilamide, with only 1 fatality. In 2 patients there was jaundice caused by toxic hepatitis. In 54 of the 58 cases the temperature fell to normal and the patient was apparently well 48 hours or less after administration of the drug had been started. In 49 cases this favorable result occurred within 36 hours, and in 35 cases within 24 hours. Compared to specific antipneumococcus serum therapy, sulphapyridine had a particular advantage in the treatment of the pneumonias of infancy and childhood, for it can be administered as soon as the diagnosis is made, thus avoiding the 1 day delay usually met in children before the pneumococci can be typed. Successful typing is often impossible in infants and children as was evidenced in the fact that only 14% of this series could be typed.

From a review of the literature it is found that the favorable reports on the use of the sulphanilamide group of preparations greatly predominate over the reports of untoward effects, blood dyscrasias and other sequelæ of its use. In fact, many of these are transient and clear up promptly after the use of the drug has been discontinued. Fatal complications have been the exception and deaths and serious after-effects are proportionately no greater, for instance, than those following the use of the arsphenamine preparations. Some disturbances in susceptible individuals should be expected in the use of any powerful chemotherapeutic agent. While its use is not recommended for indiscriminate application, especially in conditions of mild infections easily controlled by less powerful drugs, in severe infections the possibility of any complication or ill-effect need not be considered, as the primary requisite is the combating of the threatening infection. In the long run it will be found that the ill-effects from the drug are minimal after all.

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PHYSIOLOGY

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Studies on the Detoxication of Local Anesthetics. HELENE WASTL (Department of Anatomy and the Research Foundation, Hahnemann Medical College). Toxic doses of procaine hydrochloride and butyn sulphate were injected intramuscularly into guinea pigs and mice. It was observed that the signs of toxicity were delayed in onset and briefer in duration, and that the mortality incidence was decreased, when various calcium salts were injected simultaneously with the local anesthetics; this protective action was found to occur when the two substances were injected at separate sites as well as when they were injected after preliminary mixing.

The degree of protection provided by the calcium salts shows a direct logarithmic relationship with the size of the dose employed. The majority of the salts employed (the benzoate, levulinate, salicylate and lactate) are relatively less effective when injected separately than when they are injected after mixture, but this relationship is reversed in the

case of the gluconate. In all instances the protection provided against butyn sulphate is superior to that provided against procaine hydrochloride.

Neither the molecular weight of the calcium salt nor its hydrogen ion concentration plays a rôle in the degree of protection which it provides, but the degree of ionization appears to play a certain rôle when it is injected along with the local anesthetic. When injected after preliminary mixing, the salts, in order of decreasing effectiveness, rank as follows: benzoate, salicylate, levulinate, lactate, gluconate; when injected separately they rank (against procaine) benzoate, gluconate, salicylate, levulinate, lactate and (against butyn) benzoate, gluconate, levulinate, salicylate, lactate. As a practical clinical matter only two of these salts (the levulinate and the gluconate) are sufficiently non-irritant to permit of subcutaneous or intramuscular injection; of the two, as the above ranking demonstrates, the levulinate is to be preferred if it is to be injected as part of the anesthetic mixture.

The Effect of Insulin on the Electrical Activity of Nerve. JOSEPH HUGHES (Institute of the Pennsylvania Hospital). The action of insulin on the after potentials of the cat's phrenic nerve has been studied. The nerves used in these experiments were mounted in a chamber through which was passing a mixture of 5% CO_2 and 95% O_2 according to Lehman's technique. The after potentials were recorded on a cathode ray tube.

After obtaining control pictures the nerve was then immersed in Krebs-Ringer solution containing zinc-free insulin. The pH of this solution was 7.4 to 7.45.

Solutions containing 0.002 of a clinical unit of zinc free insulin per cubic centimeter produced a change in the after potentials after 1 hour of soaking. This effect consisted in a shortening of the negative and deepening of the positive wave. The spike was usually unchanged. This effect has been observed with dilutions as great as 0.0002 clinical units per cubic centimeter. It is lost at higher dilutions. With dilutions of 0.2 clinical units per cubic centimeter undulating waves appear in the after potentials. These changes occur at a pH of 7.4. They were abolished by decreasing the pH to approximately 6.4 to 6.6 by means of increasing the CO_2 flow into the nerve chamber. Excitability curves, run after the insulin effect was established, showed that the irritability of the nerves paralleled the after potential changes. Nerves soaked in insulin which had been inactivated by mean of NaOH failed to show these after potential changes.

The Chemical and Physical Properties of the Gonadotrophic Hormone of Human Pregnancy Urine. SAMUEL GURIN, CARL BACHMAN and D. WRIGHT WILSON (Departments of Physiological Chemistry and Obstetrics and Gynecology, University of Pennsylvania). Several fractionation methods have been employed for obtaining pregnancy urine gonadotrophic preparations assaying 4000 minimal effective doses (M.E.D.) per milligram when tested in the post-partum rabbit. The activity of these preparations could not be raised by further chemical manipulation. Analysis of such products indicates that they are glyco-proteins containing 50% carbon, 7% hydrogen, 12% nitrogen, 10 to 12% galactose and 5 to 6% hexosamine.

Upon examination in the Tiselius electrophoresis apparatus, a preparation containing 4000 M.E.D. per milligram showed a single mobile component with a mobility equal to 4.85×10^{-5} cm.^{2} sec.$^{-1}$ volt.$^{-1}$ The substance was therefore essentially homogeneous with respect to electrical charge. The mobile protein, upon recovery, was biologically active and had the composition of a glycoprotein.

The same preparation likewise produced a single sedimenting band indicative of homogeneity when examined in the ultracentrifuge, as did a second preparation of similar biological activity prepared by a different method. The sedimentation constant (5×10^{-13} cm. dynes^{-1} sec.$^{-1}$) suggests a minimum molecular weight of 60,000 to 80,000 if the molecule is assumed to be spherical.

These observations indicate that hormone preparations containing 4000 M.E.D. per milligram are essentially pure.

The Functions of the Carotid and Aortic Bodies. Carl F. Schmidt, J. H. Comroe, Jr., R. D. Dripps, Jr., and P. R. Dumke (Laboratory of Pharmacology, University of Pennsylvania). Investigations in various laboratories (including this) show that the chemoreceptors of the carotid and aortic bodies are only a part of the mechanism by which the respiratory and circulatory responses to chemical changes in the blood are brought about. Their functions must therefore be ascertained by obtaining an adequate amount of valid quantitative data regarding their sensitivity and the size of their contribution to the total response. Investigations of the past 3 years, and still continuing, justify the following statements:

1. The impulses from the chemoreceptors are positively stimulant to the respiratory, vasomotor, and cardio-inhibitory centers; stimulant responses are not due to removal of an influence previously inhibitory, as in the case of the impulses from the pressoreceptors of the carotid sinus and aortic arch.

2. The thresholds of the carotid chemoreceptors to changes in CO_2 tension and acidity are about 10 mm. Hg and pH 0.1 respectively, in lightly anesthetized, vagotomized dogs subjected to saline profusion of both carotid bodies. The corresponding thresholds of the respiratory center, in animals similarly prepared, are of the order of 3 mm. and less than pH 0.02. The threshold of the chemoreceptors to anoxia is certainly lower than that of the center, if indeed the latter is stimulated at all.

3. Direct experiments on dogs have given no support to the contention of Heymans and Bouckaert (Ergeb. d. Physiol., **41**, 28, 1939) that the carotid chemoreceptors are more sensitive and more rapid than the respiratory center in responding to changes in arterial CO_2 tension. The same is true for the statement by Euler and Liljestrand (Skand. Arch. Physiol., **74**, 101, 1936) that the chemoreceptors are continuously stimulated by the CO_2 tension existing in arterial blood under resting conditions.

4. There is some tonic activity in the carotid bodies of some animals without anoxemia, hypercarbia, or acidosis, as shown by reflex respiratory depression on cooling the fluid perfusing the carotid bodies, but this occurs even when the fluid is greatly below the normal resting content with respect to any known chemoreceptor stimulant (O_2 tension

over 150 mm., CO_2 below 1 mm., and pH 7.5). This may be due to the presence of receptors activated by temperature changes in the carotid bodies in such cases (Schmidt, Dumke, and Dripps: Proc. Soc. Exp. Biol. and Med., **42**, 31, 1939).

5. The conclusions derived from our previous studies (Am. J. Physiol., **102**, 94, 1932; **121**, 75, 1938; **127**, 76, 1939)—that chemoreceptor reflexes are less sensitive than the center to CO_2 and pH, that they constitute an accessory, supporting mechanism brought into play only in emergencies such as anoxemia, unusually great increases in CO_2 tension and acidity, or poisoning by drugs such as cyanide, lobeline, and so on—are therefore reaffirmed.

Influence of Organic Compounds Upon the Secretory Activity of the Frog Liver. Rudolf Höber and Elinor Moore (Department of Physiology, University of Pennsylvania). The ability of the isolated Ringer perfused frog liver, to concentrate dyestuffs in its secretion several hundred times, can be abolished entirely and reversibly by replacing in the Ringer solution about $\frac{1}{8}$ of the NaCl by the isosmotic amount of a surface-inactive lipoid-insoluble hydrophilic non-electrolyte (disaccharide, hexose, pentose, polyhydric alcohol, amino acid, acid amide) or electrolyte (salts of lower fatty acids, hydroxyl carboxylic and dicarboxylic acids). This effect is not dependent upon changes in the perfusion rate. The opposite effect, promotion of secretory activity, can be brought about by polar-nonpolar electrolytes (salts of higher fatty acids, bile acids and other aromatic carboxylic acids, aromatic sulphonic acids) and surface-active non-electrolytes (alkaloids, digitonin, anesthetics). However, reversibility of this effect cannot be regularly observed, since cytolysis is frequently the end result. Suitable concentrations of inhibitory and promoting substances, simultaneously applied, counteract each other. Inhibitory and promoting substances, in general, exhibit opposite effects upon the dispersion of colloids (starch, lecithin, gelatin).

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